PROGRESS IN CLINICAL MEDICINE

By VARIOUS AUTHORS

EDITED BY

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SECOND EDITION

WITH 43 ILLUSTRATIONS



LONDON

J & A CHURCHILL LTD

104 GLOUCESTER PLACE W 1

1952

First Edition	1948
Reprinted	1948
Second Edition	1952

Printed in Great Britain

PREFACE TO THE SECOND EDITION

ALTHOUGH purpose and method remain unchanged and we have again limited ourselves to advances which we believe to be of permanent clinical value the three years which have passed since the appearance of the first edition have seen so many new developments in clinical medicine that the present volume is almost entirely re written

Again we have omitted much that is new especially work in highly specialised fields or in very rare diseases unlikely to be of more than occasional interest to the general physician More debatably we have made little attempt to deal with the fringe of immediate medical progress but have devoted the available space chiefly to the presentation of methods already tested and used in the larger hospitals

The change of emphasis from military to civil pre-occupations is evident in the discard of chapters on Tropical and Venereal Diseases to make space for Industrial Medicine and Physical Treatment in Mental Illness Amongst subjects dealt with for the first time are cerebral angiography electrolyte and water balance cortisone and A C T H hypersplenism toxoplasmosis electrocardiography Parkinsonism and the newer antibiotics

If a general observation is permissible it is in relation to the great contributions made to progress in many fields of medicine by our surgical colleagues We make no apology for the discussion in several chapters of therapeutic measures ordinarily considered surgical As an increasing number of medical conditions come within the scope of surgical treatment it behoves the physician to study critically the uses and limitations of operative measures if only because he is so often called upon to take the initial decision for or against surgery

Our thanks are due to Dr James Bull of the National Hospital Queens Square for Figs 24 to 29 the Editor of the *St Thomas's Hospital Reports* and Dr Forest Smith for Fig 30 the Editor of the *Lancet* and Dr Hill for Figs 11 16 17 18 and 20 the Editor of the *Post graduate Medical Journal* and Dr Samuel Oram for Fig 15 the Editor of the *American Heart Journal* and Dr Myers for Fig 19 the Editor of the *American Journal of Ophthalmology* and Professor Ida Mann for Figs 31 and 32 the Editor of the *Quarterly Journal of Medicine* for Figs 33 and 34 the Editor of the *Proceedings of the Royal Society of Medicine* for Table II the Editor of the *Lancet* Dr Rice Oxley and Dr Truelove for the data on ulcerative colitis the Editor of

Surgery Gynæcology and Obstetrics and Mr Alison for the quotation on œsophagitis Mr Brocl for Figs 35 to 37, and Dr Macoun for his valuable work in proof reading and indexing

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CHAPTER I

THE CONTROL OF INFECTIONS

by

MAURICE MITMAN

Sources and Modes of infection Immunisation Chemotherapy—Antibiotics and Sulphonamides

SOURCES AND MODES OF INFECTION

In few fields of medicine has empiricism been more fully confirmed by subsequent scientific discovery than in the field of infection Dust has long been regarded as a harbinger of disease cleanliness has been perennially next to godliness fresh air and sunlight into houses is no new town plan and poverty and overcrowding are social diseases long associated with epidemics

Since the beginning of the 20th century and despite two world wars there has been a remarkable decline in deaths from infectious diseases as the following amazing figures (quoted in *Lancet* 1944 I 317) show —

Number of Deaths in England and Wales per million living under fifteen years of age

Years	Scarlet Fever	Whooping Cough	Measles	Diphtheria and Croup
1856–60	[illegible] 201	1 398	1 185	1 397
1939	71	14[illegible]	3[illegible]	431

The tempo of the decline has been accelerated in the case of diphtheria by the introduction of mass immunisation so that the figure for England and Wales for 1946 was 67 The mode of infection of these respiratory diseases is now clearer At the end of the nineteenth century Flugge propounded his theory of the transference of infectious

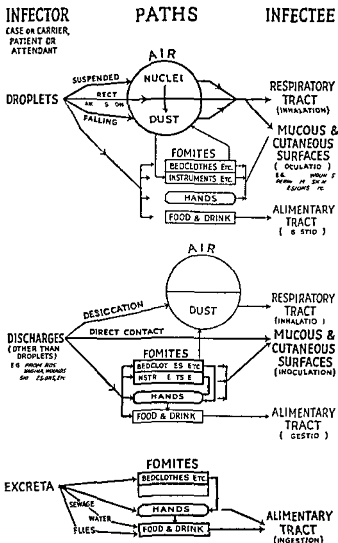
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droplets from one respiratory tract to another Not until Wells (1934) postulated droplet nuclei was the more indirect transference under stood

The source of infection is almost always a case or carrier of the disease The path from infector to infectee may be direct or devious but this is not synonymous with "direct" or "indirect" contact—the indefinite terms which usually mean "proximity" or 'distance' from infector During the passage of organisms from infector to infectee air, fomites hands of attendants and food and drink may be contaminated Entry to the new host is effected through the respiratory tract by inhalation through the alimentary tract by ingestion and through the skin or mucosa by inoculation or implantation The mode of entry serves to classify the infectious disease and to determine the measures used in its control Infectious material is expelled from the body of an infector in discharges or excreta The most important discharges concerned in the transfer of respiratory disease are the droplets expelled from the mouth and nose during sneezing coughing laughing or talking In sneezing the forceful expulsion of air through the narrowed orifice of the mouth atomises the mucous secretions of the upper respiratory tract The resulting droplets which are expelled chiefly through the mouth and only to a small extent through the nose are infected with the flora of the upper respiratory tract Their number is enormous—from 20 000 to 100 000 for an average sneeze Their size is variable The greater the velocity of the air stream and the smaller the orifice the more efficient is the atomisation and the smaller the droplets Commonly two thirds of them are less than 100 μ in diameter (i e 1/10 milli *metre) but their size varies from 7μ to 1 000 μ* Size influences their subsequent fate The larger droplets fall to the ground usually within three feet of the sneezer The smaller ones remain suspended in the air for a variable period and may be disseminated by air currents to distant parts of a room From the moment of expulsion droplets undergo rapid evaporation which reduces their size and allows them *to remain air borne* Wells (1934) considers 100—200 μ as the dividing line between droplets likely to fall and those likely to remain suspended is *droplet nuclei* Although deposition of such droplets occurs the rate is slow and about 10 per cent are still suspended eight hours after their expulsion

It is these suspended droplet nuclei which are chiefly responsible for *aerial infection* The relative importance of dust in the transfer of disease is still undetermined It is certain that during bed making and other ward activities the bacterial load of the air is increased enormously and that dust suppressive measures such as oiling bed clothes and floors reduces the load enormously but the evidence of

reduction of clinical disease although positive is more limited Hare and McKenzie (1946) stress the importance of clothing in the transfer of dust borne infections but Wells (1944) considers such infections do not explain the epidemic pattern of disease



PATHS OF INFECTION
(*From Harries and Mitman s Clinical Practice in Infectious Fevers E and S Livingstone*)

Infected air is usually inhaled by the new host but it may be implanted on wounds burns or instruments or infrequently it may

be deposited on food and ingested The fate of inhaled droplets and dust particles depends on their size The largest particles are deposited in the upper respiratory tract and only the smallest 5 μ or less in diameter, succeed in reaching the lungs The physical factors concerned in the deposition of particles in the respiratory tract are turbulence centrifugal force gravity, adsorption and the tortuous character of the conducting channel—the *nose and upper respiratory tract* Turbulence is the sudden checking of the air current which occurs most strikingly in the pharynx The removal of foreign particles from the lung is effected by ciliary action by peristaltic movements of the bronchi and by coughing *In the alveoli, phagocytes or dust cells* contribute to the removal (Robertson 1943)

The purification of intramural air is thus significant in the control of respiratory infections Three principal methods are available—ventilation dust suppression *by oiling bedclothes and floors, and* aerial disinfection by aerosols or ultra violet light Ventilation is expressed as the number of changes of air (turnovers) per hour or as the volume of air per occupant The British Paediatric Association *regards eight to ten changes per hour as good Theoretically* each turnover means the addition of the same volume of air to the room and reduces the contamination by $\frac{1}{e}$ where e is the base of the natural logarithm (2 718) One turnover per hour reduces the bacterial load *to a half in 40 minutes* four turnovers do it in ten minutes and ten turnovers in four minutes An overcrowded room or railway carriage cannot be adequately ventilated because the rate of addition of respiratory organism to the air is too high Overcrowding in hospital is avoided by adequate bed spacing which reduces appreciably the incidence of nosocomial infections The British Paediatric Association recommends not less than nine feet between beds in children s wards in fever hospitals the distance is 12 feet In all accommodation for children a proportion of cubicles is essential the most satisfactory type being the cell or chamber with partitions reaching the ceiling and with separate ventilation Much less efficient are three quarter cubicles with incomplete partitions seven or eight feet high

Germicidal ultra violet radiation produces an air disinfection *equivalent to many turnovers per hour A simple but special* cold mercury vapour lamp with an emission band at 2 537 Angstrom units is required (*vide Aerobiology* 1942 Mitman, 1945) Irradiation may be direct but more frequently it is indirect the ceiling being irradiated and convection currents carrying the infected air upwards *to be* disinfected Direct radiation or a combination of direct and indirect may be used to form germicidal curtains around beds barriers across corridors and sterile fields in operating theatres Ultra violet light has poor penetrating power *and its efficiency against organisms*

in dust is low. Sunlight and even diffuse daylight (Garrod 1944) are germicidal, dust near windows being freer from organisms than that in dark corners and near the beds of infected patients.

Suppression of dust by oiling has been more successful when applied to bed clothes than to floors. Only wooden floors are suitable for treatment and they must be scrubbed before the oil—spindle oil or a proprietary preparation like "Nuvol"—is applied. The process has to be repeated at monthly intervals. For clothing technical white oil and various proprietary preparations, e.g. Fixanol C, Teepol, Triton E, Fractol A, CTAB have been used. The object is to deposit 2.5 per cent. of finely divided oil on to the clothing so that infectious particles adhere and are not raised as dust during bed making. The oil is added during laundering and is scarcely perceptible to the patient. The hardness of the water and its pH influence the successful application of most oils. Wool and cotton goods require different treatment. The process must be repeated at each washing, although claims have been made for oil emulsions which last through several washings. There is evidence of the value of oiling in reducing streptococcal infections (Wright 1945) but not the common catarrhal infection of the upper respiratory tract.

A special atomiser is needed to produce the germicidal mists called aerosols. It was originally claimed that they exerted their action not only by virtue of their chemical nature but also because of their physical state of fine atomisation. Recently it has been widely accepted that the vapour is the active physical form of the germicide. Hypochlorites, the higher phenols such as resorcinol and glycols have been used. Glycols have the valuable property of persistence but require a relative humidity of 40–60 per cent. for maximum efficiency (Robertson *et al.* 1944).

Tracing the sources and paths of infection has been much facilitated by laboratory methods for typing organisms. The gravis, mitis and intermedius strains of diphtheria bacilli can be identified by cultural and biochemical methods. A great advance was made when hæmolytic streptococci were classified into groups and types by serological methods. One of the first fruits of this work was the knowledge that many of the complications of scarlet fever were cross infections with a type of streptococcus different from that responsible for the original attack of the disease. The considerable incidence of *bacteriological* cross infection as distinct from *clinical* cross infection in hospital was revealed in all types of wards. A further classification is now possible by the method of "phage typing," in which bacteriophages are used for detecting different lysosensitivities of certain types of organism. In typhoid fever 24 types and sub types are described and in para typhoid fever B eight types and sub types (Felix 1944). Sonne

be deposited on food and ingested The fate of inhaled droplets and dust particles depends on their size The largest particles are deposited in the upper respiratory tract and only the smallest 5 μ or less in diameter succeed in reaching the lungs The physical factors concerned in the deposition of particles in the respiratory tract are turbulence centrifugal force gravity, adsorption and the tortuous character of the conducting channel—the nose and upper respiratory tract Turbulence is the sudden checking of the air current which occurs most strikingly in the pharynx The removal of foreign particles from the lung is effected by ciliary action by peristaltic movements of the bronchi and by coughing In the alveoli phagocytes or dust cells contribute to the removal (Robertson 1943)

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IMMUNISATION

Diphtheria Active immunisation as a preventative measure has been consolidated since mass immunisation provided such a marked impetus to the decline in diphtheria Current prophylactics are all preparations of diphtheria toxoid In this country alum precipitated toxoid (A P T) is the usual choice Two doses are essential to obtain full advantage of the much greater antigenic stimulus provided by the second injection which acts as a secondary stimulus The usual doses are 0 2 millilitres and 0 5 millilitres by deep intramuscular injections at intervals of four to six weeks but the doses could with advantage be reversed because reactions are less common after the primary stimulus and the quantity necessary to act as the secondary stimulus is small The most suitable age for immunisation is 8 to 12 months unless the diphtheria prophylactic is combined with whooping cough vaccine (*vide infra*) A small reinforcing injection is desirable two or three years after the initial injection and again on joining school at five years of age with possibly one other at 8 to 14 years of age In these older children it is desirable to perform a Schick test *before giving a boosting injection* In a *mass immunisation* campaign Schick tests are dispensed with apart from sample tests as a check on the efficiency of the prophylactic In older patients liable to reactions toxoid antitoxin floccules (T A F) three doses of one millilitre at three or four weekly intervals give less trouble but are not so efficient In Canada formol toxoid is still used The Moloney test for detecting hypersensitivity to the toxoid is identical with the pseudo reaction of the Schick test which should be performed in preference to it Although the antigenic strength of diphtheria prophylactics is expressed in Lf flocculating units the method is not

dysentery bacilli have been classified into 14 types and the method has also been used for the typing of staphylococcus and soil bacteria

Much importance is attached to staphylococcus aureus as a cause of widespread pyogenic infections and to the nose as the site of carrying the organism Not only wound infections but generalised furunculosis and food poisoning have been traced to the transfer of staphylococci by hand from the nose to the skin or to food Parsons (1944) traced maternal mastitis and abscess, and infantile infections of the skin and elsewhere to staphylococci derived from the noses of nurses The carrier rate among healthy persons is as high as 20–45 per cent and the frequency of handling the nose, even in the socially irreproachable is surprising

The prevention of food poisoning depends considerably on kitchen hygiene Those engaged in the storage preparation and sale of food must observe cleanliness in themselves their place of work and their utensils The handling of food must be reduced to a minimum Prepared meat milk cream and egg products and ice cream are most suitable media for the growth of food poisoning organisms The period of incubation after infection by the food handler allows the pathogens to multiply to numbers capable of causing a clinical infection Such articles should therefore, not be allowed to stand about in hot kitchens, but should be refrigerated

The memorandum of the Medical Research Council on cross infection in Hospitals, points out that cross infection is most apparent and most dangerous among infants and children in general and fever hospitals, but adults are also liable to acquire such infections, particularly those with wounds burns and placental sites Wards in which infections of the ear nose and throat are treated are most dangerous but even in ' clean ' surgical and maternity wards measures must be taken to prevent the spread of infection *Chemoprophylaxis must not* be used as a substitute for good medical and nursing practice Good ventilation, proper bed spacing equipment for efficient sterilisation or disinfection and an adequate staff trained in the proper nursing technique are the chief recommendations

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free from the most serious drawback to human convalescent serum the danger of homologous serum jaundice Cockburn *et al* (1951) report a case of serum jaundice in a boy injected with gamma globulin prepared from an icterogenic batch of plasma Cohn s fractionation of blood plasma depends on the methods of high speed centrifugalization electrophoresis (for gamma globulins) diffusion viscosity and precipitation by iso-electric charges The products obtained include albumen used for restoration of blood volume fibrinogen prothrombin iso-hæmagglutinins Rh antibodies and α β- and γ globulins Gamma globulin has been successfully used in passive immunisation against measles and infective hepatitis It is estimated that gamma globulin is six times as potent as convalescent measles serum and may be given to attentuate or to prevent attacks

Vaccination against Smallpox The old method of vaccination by a linear insertion has been displaced by the multiple pressure method which now has official backing (Min of Health Memo 1948) Many claims have been made for the superiority of the method which consists in inoculating the lymph by 10 to 20 pricks using a needle not at right angles to the surface of the skin but parallel to it Enough pressure is exerted to depress the skin at the point of the needle Probably the virtue of the method lies in the fact that it ensures a minimal penetration of the epidermis at a number of points The interpretations placed upon the resulting reactions are still debatable Officially three types of reaction are recognised

(1) The primary reaction—vaccinia—maximum on 7th to 10th day occurs when there is no immunity or when immunity has waned

(2) The accelerated reaction—vaccinoid—maximum on 5th to 7th day occurs in the revaccinated who have lost some but not all of their resistance

(3) The immediate reaction which is maximum on the 2nd or 3rd day and is considered to be evidence of immunity

No reaction is regarded as a failure in the technique of vaccination Mitman (1947) among others disputes these interpretations He maintains there are only two specific reactions to the live lymph—vaccinia in the susceptible and vaccinoid in the partially immune vaccinoid reactions are aborted not accelerated No reaction at all occurs in those who are immune Superimposed on these reactions are those due to sensitivity in subjects who have previous experience of lymph They precede a vaccinoid reaction or even an ordinary vaccinia but in the immune they are the only reaction—hence the confusion with immunity No inferences as to the immunity of the subject should be drawn from immediate reactions for they can occur even with inactivated lymph

satisfactory Holt (1947) recently introduced a new prophylactic—purified toxoid aluminium phosphate precipitated (P T A P) in which antigenic potency is related to the quantity of mineral carrier (aluminium phosphate) and can be expressed in terms of it

Whooping Cough American results with whooping cough vaccines have not been reproduced in Britain and a satisfactory antigen has not yet been established Recent trials however suggest that a more efficient one is now available Prophylactics used include a simple vaccine (Sauer) prepared from smooth strains of organisms in the correct, antigenic phase 1 and under correct conditions of cultivation to preserve antigenic power an alum precipitated vaccine and a detoxified pertussis antigen The number of doses and their size is still debated Commonly 80 000 million to 120 000 million organisms are distributed over three doses at three weekly intervals Because of the uncertainty of results most Local Authorities are not prepared to embark on a campaign for mass immunisation They may be willing to combine whooping cough with diphtheria immunisation so that without increasing the number of injections a sound promise of protection can be given against diphtheria and a much more guarded promise of protection or of attenuation against whooping cough The combined prophylactic contains A P T and alum precipitated pertussis vaccine Three doses—0 5 millilitres 0 5 millilitres and 1 0 millilitres—are given every four weeks starting at three months

Poliomyelitis following injections Geffen (1950) McCloskey (1950) and Martin (1950) all observed an association between the limb inoculated with diphtheria or whooping cough prophylactic and the site of maximum paralysis of poliomyelitis which subsequently developed In some cases the disease was limited to the injected limb e g an injection into the arm was followed after an incubation period by a shoulder girdle syndrome For this reason some local authorities are suspending their immunisation campaigns during the prevalence of poliomyelitis

Measles The outstanding advance in passive immunisation in recent years has been the separation of gamma globulin from blood plasma (Cohn 1941 1945) In unconcentrated immune sera derived from animals antibodies are to a considerable extent attached to globulins When serum was concentrated the globulins were salted out and re dissolved so that the potency of the serum was considerably increased In refined serum the big molecule to which antitoxin was attached was split up or disaggregated by a process of protein digestion This further purified and concentrated the serum Cohn s work however promises to provide a product of human serum which is 25 times as concentrated as adult blood and which prepared from a large enough pool may prove a common passive prophylactic

TABLE I

Antibiotics of choice in various infections

(Compiled chiefly from Long *et al.* 1950)

A = Aureomycin C = Chloramphenicol P = Penicillin S = Streptomycin
Sulf = Sulphonamides T = Terramycin
Combinations of antibiotics used in severe infections are hyphenated e.g. P-A

Infection	First Choice	Second Choice	Third Choice	No Value	Value not known
Anthrax	P or A			CS	T
Brucella (inc. Bact. tularense)	A or C	T + S	S + Sulf	P	
Cholera				PS	ACT
Clostridial					
Gas gangrene	P			S	ACT
Tetanus	P			ACST	
Diphtheritic	Antitoxin - P			ACS	T
Gram neg. bacillary					
Bact. coli	C or A	S or T		P	
pneumoniæ	A	C	S or T	P	
Proteus	S			ACP	T
G neg. meningitis	S-A-C				
G neg. subac. bacterial endocarditis	S-A-C				
Hæmophilus					
H. influenzæ meningitis	A - Sulf	C - Sulf	S - Sulf	P	T
H. Pertussis	?A or ?C	?S		P	T
H. ducreyi	C or A	S		P	T
Listerella	A			PS	CT
Neisserian					
N. meningitidis	Sulf + P	Sulf - A	Sulf + C	S	T
N. gonorrhœæ	P	S	A or C or T		
Pasteurella					
B. pestis	S - Sulf			P	ACT
Pneumococcal	P	A	S or T		
Acute bacterial endocarditis	P-A				
Meningitis	P-A				
Salmonella					
S. typhi	C			APST	
Others	?C				APST
Shigella	C or A			PS	T
Spirochætal					
T. pallidum	P	C or A or T		S	
Leptospira icterohæmorrhagiæ	?P	?A		S	CT
Leptospira canicola	P	A or C	S		T
Staphylococcal	A	P	T or S	C	
Severe infections	A-P				
Subacute bacterial endocarditis	A-P				
Meningitis	A-P				
Streptobacillary	S			P	ACT
Streptococcal					
β hæmolytic	P	A or S	C		T
ac. bact. endocarditis	P-A				
α hæmolytic	P	A or S		C	T
subac. bact. endocarditis	P-A				
non hæmolytic	P	A		CS	T

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CHEMOTHERAPY—ANTIBIOTICS AND SULPHONAMIDES

In no field of clinical medicine has progress been more rapid than in the discovery and development of the antibiotics Sulphonamides the astonishing discovery of the pre war years were completely overshadowed when the amazing penicillin was developed during the war As recently as 1950 Garrod wrote Penicillin being the perfect chemotherapeutic agent there is no need for any other except in infections insensitive to it Yet within a few years of its discovery this wonder drug ' has been displaced as the antibiotic of choice in a number of infections A striking example is afforded in staphylococcal infections The advent of penicillin the first effective drug against the organism was hailed as a major advance in treatment Resistant strains emerged to limit the value of the discovery When streptomycin appeared it became the second line of attack to be used whenever penicillin failed or caused sensitisation reactions Aureomycin when supplies became available quickly displaced streptomycin as the second choice and has now displaced penicillin as the first choice (see table I)

The source of antibiotics is of interest Although the higher fungi are potent producers of antibiotics only penicillin has been found sufficiently non toxic to be useful The soil has become the source of the newer antibiotics Except for anthrax tetanus and other clostridia, the soil is relatively free of pathogens This freedom depends on the action of inhibitory substances derived from non pathogens and constitutes the basis for the search for antibiotics The Order *Actinomyces* especially the Family *Streptomyces*, has been particularly fruitful Streptomycin was derived from *Streptomyces griseus* chloramphenicol from *Streptomyces venezuelæ* aureomycin

Drug Rashes All these drugs are capable of causing rashes streptomycin and penicillin more frequently than aureomycin and chloramphenicol Toxic rashes due to sensitisation to streptomycin and penicillin appear to be increasing in frequency Within ten days of a course of treatment or even after a single dose generalised erythema urticaria or erythema multiforme may appear A local reaction at the site of injection may occur Penicillin administered as an aerosol or by injection may cause a spasmodic allergic reaction in the respiratory tract These manifestations may be associated with general disturbance pyrexia and joint pains and may last for several days Antihistamine drugs provide some relief The drug should be stopped on the appearance of a rash Streptomycin constitutes a definite occupational hazard for nurses pharmacists laboratory technicians and anyone concerned with the administration or handling of the drug Rubber gloves should be worn as a prophylactic The hands should be washed thoroughly after possible contamination

Allergic symptoms may be due to the procaine in procaine penicillin preparations (*vide infra*) If suspected an intradermal test using 0 1 ml g 1 per cent solution of procaine hydrochloride will reveal sensitivity

Gastro intestinal Disturbance Nausea vomiting and diarrhoea are the commonest side effects of therapy with aureomycin terramycin and chloramphenicol *The looseness of the stools is in part attributed* to the disturbance of the bacterial flora of the colon and in part to impurities Purer preparations are reducing the incidence of gastro intestinal disturbances When they occur the dose of the drug should temporarily be reduced by a half and given at shorter intervals e g three hourly instead of six hourly or if a greater reduction is necessary the six hourly intervals should be maintained with the smaller dose

Penicillin Penicillin G is now used almost exclusively because of its purity The action of penicillin is chiefly if not exclusively on multiplying organisms There is evidence that intermittent concentration of the drug has some virtue in that the intervals permit the surviving organisms to multiply and become susceptible to the next high concentration of the drug (Eagle and Musselman 1949) Nevertheless the present tendency in therapeutics is to maintain an optimum concentration with a preparation which reduces the necessity for frequent injections Garrod (1950) points out that penicillin is unique in that there exists an optimum concentration beyond which any increase will be useless and may indeed be detrimental In practice however dosage is determined empirically and not by estimation of blood concentration

Several methods are available for prolonging the effect of a single injection of penicillin The simple method of giving a large dose of a

Table 1—*continued*

Infection	First Choice	Second Choice	Third Choice	No Value	Value not known
Streptococcal —*cont*					
all enterococci	A	P		CS	T
enterococcal sub acute *bacterial* endocarditis	P S A				
Tuberculosis	S (+para amino salicylic acid)				
Fungal					
Actinomycosis	P + Sulf			S	ACT
Parasitic					
Ac amoebic dysentery	A			PS	CT
Rickettsial	C or A			PS	
Trichomonas vaginalis	A (A locally)			PS	CT
Viral					
Common cold				ACPST	
Chicken pox				PS	ACT
Hepatitis infectious				PS	ACT
Herpes simplex	?A			PS	CT
Herpes Zoster	AC			PS	T
Infectious Mononucleosis				ACPS	T
Influenza				ACPST	
Kerato conjunctivitis epidemic	?A			PS	CT
Lymphogranuloma venereum	A or C	P + Sulf		S	T
Measles				PS	ACT
Mumps				ACPS	T
Pneumonia primary atypical	C or A			PS	T
Poliomyelitis				ACPST	
Psittacosis	A or C	P + Sulf		S	T
Smallpox				ACPS	T
Stevens-Johnson syndrome	A				
Vaccinia disseminata	?A			PS	CT

from *Streptomyces Aureofaciens,* and terramycin from *Streptomyces rimosus*

All these antibiotics are active by mouth They all change the bacterial flora of the bowel by inhibiting those organisms which are sensitive to their action Aureomycin and terramycin for example cause the disappearance of coliform organisms streptococci and clostridia only yeasts micrococci and *candida albicans* remain The fæces become odourless and the elaboration of vitamins by intestinal commensals is impaired If treatment is continued for more than a few days vitamin B complex should be given to make good the deficiency Glossitis and an angular stomatitis are common manifestations of the deficiency

para aminosalicylic acid and the sulphones The treatment of miliary and meningeal tuberculosis is far from satisfactory Waksman s (1949) figure for survival 14 to 20 months after treatment is as low as 24 per cent A regimen for the treatment of tuberculous meningitis is still not settled As adjuvants to streptomycin Smith and Vollum (1950) used intrathecal tuberculin and Cathie and MacFarlane (1950) intrathecal streptokinase With both substances the beneficial action is attributed to the lytic effect of the adjuvant on the meningeal exudate thereby allowing streptomycin access to the organism Neomycin (Waksman 1950) is active against streptomycin sensitive and streptomycin resistant organisms whether the resistance is natural or acquired but it has nephrotoxic and ototoxic properties which limit its use

Chloramphenicol ("Chloromycetin") and Aureomycin These two antibiotics are now established as the first choice in many infections (see Table I) Their outstanding value lies in their ability to combat infections with gram negative organisms *Rickettsiæ* and the larger viruses against which previous antibiotics were largely ineffective They both have an impressive range of activity against pathogens There is little to choose between them Now that aureomycin is available in Great Britain it has tended to supplant chloramphenicol as the first choice except in those few infections against which chloramphenicol is outstandingly superior such as the enteric fevers and typhus It is unusual for organisms to develop resistance to these drugs and when it occurs the resistance is not common to penicillin or streptomycin Both drugs are supplied as a powder in capsules and are usually given by mouth although an intravenous form of aureomycin is available There is little evidence of toxicity apart from the gastro intestinal disorder described above

The daily dose of chloramphenicol is 55 mgm per Kgm body weight In determining the number of capsules to be given (each contains 250 mgm) a convenient approximation can be made by dividing the patient s weight in pounds by ten This gives the number of capsules to be given daily e g a patient weighing ten stone would require 14 capsules daily The daily dose is divided the intervals being four or six hours it should never exceed eight hours because of the fall in concentration in the blood In susceptible infections the response is rapid but the drug must be continued after signs and symptoms have abated or relapses will occur The dose of the drug can be halved after the febrile period In severe infections a loading dose is commonly given and the daily maintenance dose is doubled i e 110 mgms per Kgm body weight

The standard dose of aureomycin by mouth is 25 mgm per Kgm body weight every 24 hours divided into four equal doses For the

soluble salt to maintain a therapeutic level for a longer period is uneconomical Doubling the dose prolongs the effect by one third only and does not ensure an adequate level for a whole day Interfering with renal excretion by using blocking agents is not a practice which commends itself coronamide 9 grams daily is effective but its toxic effects—nausea rashes and albuminuria—have limited its use to experimental work in hospital The method in common use is the prescription of depot preparations of the drug Their object is to slow up absorption from the site of injection By their use a therapeutic level can be maintained for 24 to 36 hours The official preparation *Injectio Penicillini Oleosa* is a suspension of the calcium salt in arachis oil and beeswax It is troublesome to use because it needs warming to make it flow freely It causes pain induration and foreign body reaction It has been displaced by preparations containing procaine Penicillin is an acid and combines with procaine to form a sparingly soluble salt Because of its low solubility procaine penicillin G has depot properties It is made up either in an oily or an aqueous suspension Aluminium monostearate is commonly added to the oily suspension because it has a stabilising effect on the suspension and also because it repels water thereby delaying absorption still longer 'Avloprocil' (I C I) *is an example A soluble penicillin salt (Ca or* K) may be added to the preparation Its rapid absorption causes a high initial concentration—a loading dose—which is followed by the slower and more prolonged action of the procaine penicillin e g *Prolopen (Glaxo) The aqueous suspensions are available as a* sterile dry powder containing a suspending agent which needs to be mixed with sterile water immediately before use or as a ready prepared aqueous suspension e g 'Distaquaine (The Distillers Co) Mylipen *(Glaxo) Here again a soluble penicillin may be added to* provide a loading dose as in Distaquaine Fortified Seclopen (Glaxo) and Abbocelin R/R' (Abbot) These preparations all contain 300 000 units of procaine penicillin per ml Where a soluble salt is added the additional dose is 100 000 units per ml

Streptomycin and Neomycin The newer and better antibiotics have displaced streptomycin as the drug of first choice in all infections except those due to *M tuberculosis Ps pyocyanea* and *Proteus vulgaris* Table I shows those infections in which streptomycin is usefully combined with other drugs or constitutes a second or third line of attack The considerable limitations and drawbacks to streptomycin and dihydro streptomycin include not only the well known vestibular damage but also the ease with which organisms become drug resistant As methods of avoiding the development of resistant strains Waksman (1950) mentions intermittent administration and combination with other tuberculostatic agents Of the latter the most important are

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The standard dose of aureomycin by mouth is 25 mgm per Kgm body weight every 24 hours divided into four equal doses For the

average adult this means two capsules of 250 mgms every six hours For children capsules containing 50 mgm are available Infections should respond quickly if they fail to do so after 48 hours the dose should be doubled *Full dosage must be continued for a day or two* after the temperature has fallen and then reduced to a half Loading doses and double standard doses are indicated in severe infections and those known to be difficult to influence such as bacterial endocarditis

Aureomycin is prepared as the hydrochloride It is not very soluble and forms a strongly acid solution which causes pain on intramuscular injection A form for intravenous administration is available in vials of 100 mgm and 500 mgm The solution must be well diluted and a change made to the oral route as soon as possible because of the *likelihood of thrombophlebitis at the site of injection* The standard dose is 500 mgm intravenously every 12 hours or 300 mgm every eight hours Not more than 500 mgm should be given at a time not less than 10 ml of diluent must be used for each 100 mgm of aureomycin and the injection must be given slowly taking five minutes for *each 10 ml of the solution If it is necessary to adjust the dose* upwards it must be done by shortening the intervals from 12 to 6 hourly Intravenous therapy should be reserved for patients in hospital

Terramycin The chemical structure of this drug shows many *points of similarity to aureomycin Being amphoteric it can form a* hydrochloride and a sodium salt It is soluble in water and a solution keeps well at room temperature The drug is active by mouth as well as by injection The infections against which it is effective are listed in Table 1 It is especially active against clostridia and saprophytic mycobacteria *but has little or no action on proteus pyocyaneus* and fungi Its efficiency against brucella is enhanced when it is combined with streptomycin this is true also of aureomycin Terramycin is more active than aureomycin against some strains of organism and less active against others The dosage recommended is larger than for aureomycin 1 to 1 25 grams six hourly equivalent to 4 to 5 grams in the 24 hours The gastro intestinal irritation which occasionally occurs is said to be *less than with aureomycin and to be* controllable by administering the capsules in milk which does not interfere with the absorption of the drug

Choice of Antibiotics (See Table 1) In some instances the antibiotic of first choice is clear from the nature of the infection *although the appearance of new drugs may alter the order in a very* short time Where there is doubt as to the best drug laboratory reports on the drug sensitivities of the organism are *helpful* but the choice should be guided not decided by such reports Sensitivity is

relative and a negative laboratory report should not automatically exclude the use of a particular drug Watch should also be kept for the development of resistance when treatment is prolonged In severe and fulminating infections the quickest and most efficient method of bringing the infection under control consists in a maximum onslaught with combined antibiotics given in adequate doses Nevertheless caution is necessary to avoid overtreating patients and increasing the risk of toxic reactions Although antibiotics are in better supply they are still expensive and treatment should not be prolonged unduly With all antibiotics the natural mechanism of defence should be allowed to participate in the recovery This calls for some judgement on the part of the physician In most instances response to treatment is rapid If it has not appeared in 24–28 hours consideration should be given to increasing the dose or changing the antibiotic

Chemoprophylaxis

The drawbacks to chemoprophylaxis are the possibility of toxic reactions the development of sensitivity to the drug and the emergence of drug resistant strains of the organism They are more likely to appear when the cour e is prolonged as when drugs are given through out the winter to prevent recurrent attacks of rheumatism The newer antibiotics are less objectionable than sulphonamides and strepto mycin although a combination of the last two is still widely used and is an effective prophylactic before surgery of the colon

Mass or group prophylaxis is most usefully employed in closed communities where streptococcal meningococcal dysenteric or other infection is prevalent *Individual prophylaxis* is indicated when a special risk has been or is about to be encountered In the prevention of venereal disease a single dose of penicillin is usually adequate but in the prevention of post operative sepsis a short course of an appropriate antibiotic is desirable The width of antibiotic umbrella under which surgery is now performed varies with the surgeon but there is wide use of drugs not only in surgery of the bowel but in clean surgery The enormous reduction in the intestinal flora which can be obtained with aureomycin chloramphenicol or a combination of streptomycin and sulphasuxidine has widened the range and improved the results of major surgery on the large bowel The course should begin five days before the operation and continue for a short post operative period In clean surgery prophylaxis begins a day or two before the operation Where operations are performed in the presence of established infection the post operative course should be regarded as therapeutic and the dosage adjusted accordingly There is great use of chemoprophylaxis in minor surgical and diagnostic procedures In rheumatic subjects chemoprophylaxis is almost

obligatory before and after extraction of teeth removal of tonsils or any operative procedure on the nose and throat

Sulphonamides

Although the sulphonamides have been largely superseded by the antibiotics, they are either alone or in combination with an antibiotic the first choice in the treatment of meningococcal and dysenteric infections and they still have a place in the treatment of pneumococcal coliform and some streptococcal infections Sulphanilamide (B P) and *sulphapyridine have been abandoned* Sulphathiazole (B P) has fallen into disfavour because of its high clinical toxicity, although this objection is less pertinent when it is used in small doses in sulphonamide *mixtures Sulphapyrazine the most insoluble of the* compounds, causes frequent allergic and renal reactions and offers no advantages over sulphathiazole Sulphadimidine (B P) ('sulphamezathine sulphamethazine) and sulphamerazine (U S P) have closely similar qualities Both are adequately soluble and have a low toxicity but the former is said to be subject to substantial conjugation and plasma binding which diminish its therapeutic efficiency, it is however more soluble than the other diazines' in neutral or acid solution Sulphadiazine is still the most popular sulphonamide to be prescribed alone and it is the first choice in sulphonamide mixtures Combinations of sulphonamides are widely used (Fisk *et al* 1947 Lehr 1947 1948 1950 Ledbetter and Cronheim 1948) The principle is accepted that the therapeutic efficiency of the constituents is additive but the toxic and renal effects are not *Sensitization* phenomena depend on the repeated or maintained presence in the tissues of a critical concentration of each drug Lehr (1948) maintains *that the level in the blood should not exceed 5 mgm per cent* He attributes the greater frequency of skin sensitisation from local applications to the high local concentration reached Using mixtures the incidence of crystalluria even without alkalinisation is so low that alkalis are commonly omitted The objection to the use of alkalies is that they aggravate the tendency to decubitus calculi in those confined to bed for long periods and interfere with the resorption of the drug from the renal tubules

Lehr (1950) considers sulphadiazine and sulphamerazine qualify for first and second places in sulphonamide mixtures, and sulphadimidine *sulphathiazole or sulphacetamide for the next two places* Sodium sulphacetamide (B P) is still used by itself in 30 per cent concentration in eye drops because it is readily absorbed and almost *neutral* Since succinyl sulphathiazole (B P) and phthalylsulphathiazole are absorbed even less than sulphaguanidine (B P) they are more popular than the older drug

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CHAPTER II

INDUSTRIAL MEDICINE

by

T. A. LLOYD DAVIES

Industrial Society Rehabilitation Pulmonary diseases Toxicology Radiation

INDUSTRIAL SOCIETY

The working lifetime of two men, Thomas Legge and John Bridge, both Senior Medical Inspectors of Factories, witnessed the rise of industrial medicine from a medical curiosity invoked to prevent abuse to an accepted branch of medicine. Legge's (1934) aphorisms illuminate the fundamentals of the prevention of accidents and disease; paradoxically his great memorial, the eradication of lead poisoning as a widespread hazard, caused his resignation from the Factory Department. With exceptional clarity Bridge held that the application of measures for the prevention of a hazard should proceed contemporaneously with compensation for personal injury resulting from it. The result to-day is the list of Prescribed Diseases.

Prevention is the keynote of industrial medicine; slowly physical hazards are being brought under control but never ceasing vigilance is needed to prevent known risks from recurring and to forecast likely risks from new substances and processes.

Industry is the work of men and women and it is to the broader *needs of men and women as individuals and as members of a society* based on work that attention is now being turned. Nevertheless any practitioner who ignores the principles elaborated by the early pioneers and defined by Merewether (1948) does so at his peril. Merewether said: Industrial health is a wholly preventive special function based on law; it is predominantly but not solely medical in scope, operating

in the industrial environment and it is concerned with the individual primarily as an index of environment' The definition and enforcement of minimum standards of health safety and welfare by the Factories Acts 1937 and 1948 and their constant review and improvement by regulation are the characteristics of British industrial medicine From this basis future progress can be made

Because of the many skills involved industrial medicine can never be a specialty of medicine it is to be compared with paediatrics in which a wide knowledge of problems of medicine and other subjects is needed rather than with ophthalmology which invokes highly skilled techniques applied in a defined field Industrial medicine is the means by which the medical contribution to the well being of an industrial society is made Industrial medicine may be regarded as a branch of human ecology (Banks 1950) In fact industrial medicine might be defined as the impact between medicine and an industrial society

The report of the Dale Committee (1950) laid emphasis on the contribution of medicine toward the proper direction of industry (i e of industrial society) This specialised advice is necessary to management if health and safety and not less important efficiency are to be promoted and maintained Many of the problems facing modern civilisation arise because of the difference between an established society and an adaptive society (Elton Mayo 1945) In an established society where in return for stability the interests of the individual were by his own eager desire subordinated to the group so that technical and social skills were developed simultaneously man had time to develop the art of living In an adaptive society diverse persons casually brought together struggle to acquire new skills so that hostility aggressiveness and fear kill social skill i e the ability to secure co operation between people As Roethlisberger (1945) says the science of industry depends on men of extraordinary skill in the direction of securing co operative effort Lack of such co operative effort or in modern jargon of group morale has direct medical as well as social consequence The effect of many illnesses and even their onset may be determined by lack of social skill or morale

Ferguson (1945) after experience of the Clyde Basin Experiment has aptly remarked that the state of health or rather sub health of the industrial population is such that the majority may properly and at their choice declare themselves fit or unfit for work Family tradition trade union example habit and economic pressure all enter into the decision whether to declare fit or unfit for work Most important is keenness and liking for work To a bored disinterested workman with a monotonous job amid squalid surroundings and with uncongenial mates a minor illness is a welcome excuse to be away from work Short term sick absence is a sensitive index of morale

The Hawthorne Experiment (Whitehead 1938) in which five girl assembly workers were placed in a small group demonstrated the mutual dependence of each girl on every other though each brought dissimilar contributions to the whole Every time accustomed routines were upset the group began to rebuild itself in such a manner as to approach the condition it would have reached but for the disturbance In other words even a small society is subject to progressive evolution The attitude of the group was greatly influenced by a girl *who was able to build up new concepts out of her experiences* and doing useful things together was very productive of individual satisfaction

Too great stress cannot be laid upon the social aspects of industry Work is a social habit (Lloyd Davies 1943) *not to be at work is* abnormal Realisations of this sort are the basis of all successful organisations whether of nations armies or industries even though in the past such realisations may have been intuitive What has happened in the past few years is that a start has been made with the critical examination of the forces at work within societies or communities Health is a state of complete physical mental and social wellbeing (World Health Organisation)

Whether the approach be from the clinical or the industrial standpoint the patient—total situation complex needs to be resolved Though the clinician deals with people they have been and are being influenced by and are *influencing the culture* within which they live Trist (1950) has suggested that some of the absenteeism and *suspicion occurring in the mining industry is due to paranoic phantasies* and anxiety conditions generated because of the enforced isolation of miners working in long wall pits

Compensating projection of personal hatred into the hated system make the individual unreasonable the occupational group aggressive and society disharmonious Bitterness takes the place of mutual regard which is or should be the basis of all industrial relations Viewed in this way strikes may be said to have a cause amenable to medical study

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Fatigue Until Bartlett s (1943) crucial experiment on skill fatigue experiments in the laboratory bore little relation to industrial circumstances Fatigue in industry is a psychological condition having but slight relationship to the fatigue of muscle by repetitive stimulation In circumstances in which physical effort was minimal but mental concentration and skill very great Bartlett exhausted a series of subjects (who were so situated as in a link trainer to be part of the machine) by requiring prolonged exercise of mental effort As fatigue progressed the subject (1) made the right action at the wrong time (2) or if the right time was insisted on the wrong action (3) suffered narrowing of the stimulus field which became split into separate and unco ordinated stimuli (4) showed deterioration in the standard of performances (5) complained bitterly of proprioceptive stimuli which seemed very objectionable and distracting (6) expressed mental irritation in the most violent manner The effect of skill fatigue in causing accidents is obvious Bartlett s colleagues followed the experiment by investigation into the design of machinery both for accuracy of operation and observation More recently Bartlett (1949 1950) has propounded a theory of the means by which high mental skills (including thinking) are acquired As machines become more complex requiring the exhibition of different skills every means *will need to be taken to avoid fatigue Personal threshold to fatigue* varies widely but as a generalised statement fatigue especially if continued over a long period increases liability to mental disorientation

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Accidents and Industrial Diseases By the preferential rate for Industrial Injuries Benefit (42*s* per week for a single man compared with 26*s* a week sickness benefit) Parliament has recognised the essential difference between accidents and illness of non occupational origin and accidents and diseases which result from work The former may be said to be accounted among the normal or to a greater or less degree unavoidable hazards of living so that they are thought of as being the unfortunate act of inscrutable providence Industrial diseases are the direct consequences of the acts of man for this reason a grave sense of injustice with many emotional sequelae easily and quickly arise

REHABILITATION

During the inter-war years mass *unemployment had* economic disabilities suffered by the disabled Shortage of labour after 1940 disclosed a *reservoir of men and women who* because of injury or disease needed special training or sheltered conditions of employment if they were to undertake work continuously and successfully No mistake should be made the primary drive for rehabilitation was economic rather than humanitarian This immediately raises the question whether the provision of the Disabled Persons (Employment) Act 1944 requiring employers employing more than 20 persons to *employ a quota (at present fixed by regulation at three per cent*)* can be enforced except in times of over full employment The best *form of rehabilitation is so to place a disabled person in employment* that his disability ceases to be a hindrance

Rehabilitation schemes are of three main types (1) sheltered workshops e g Remploy factories for disabled persons and factories built in South Wales for the employment of miners certified as disabled *from pneumoconiosis* (2) protected work within normal industrial environment e g The Disabled Persons (Designated Employment) Order 1946 No 1257 reserves new appointments to the jobs of electric *lift and car park attendants to registered disabled persons* (3) *temporary* training to fit disabled persons for normal work in normal industrial conditions e g Vauxhall Motors Rehabilitation Centre for orthopaedic injuries *and Roffey Park Rehabilitation Centre for neurotic* patients Retraining (which is to be distinguished from rehabilitation) may accompany any of these schemes The main problem is whether a skilled workman can be retrained for unfamiliar work and if so at what stage in his career and at what age? When so trained can he achieve satisfaction in it?

Rehabilitation is not a substitute for bad medical and surgical treatment *Though much attention is given to industrial details and the* re-establishment of old skills or the acquisition of new skills rehabilitation is a problem in morale Admittedly work is a great support for morale but *good morale the natural outcome of good medical and nursing care* is needed before work is possible In a study of the results of treatment of peripheral nerve injuries (which normally require long and persistent treatment) *Russell Davis (1949)* has made the most important contribution to the art of rehabilitation By noting that recovery was best the sooner the objective of treatment was defined and made apparent to the patient he has struck at the vague humanistic hopes that surround many rehabilitation schemes

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* For sea going employees in shipping and fishing industries the quota is 0 1 per cent

PULMONARY DISEASES

Pneumoconiosis

Pneumoconiosis means dust on the lung The National Insurance (Industrial Injuries) Act 1946 restricts pneumoconiosis to mean fibrosis of the lung due to silica asbestos and other dusts and includes dust reticulation Pneumonitis is employed to denote inflammatory conditions arising from the inhalation of dust The distinction is not clear as claims to include bagassosis in either group might be made

Silica If four fundamental facts are remembered much of the confusion surrounding silicosis disappears (1) Silica is ubiquitous it is liable to and does occur in dangerous amounts in nearly every industrial process especially those employing ores or earths Every dust should be regarded as containing silica in harmful quantities (as little as ½ per cent may cause silicosis) unless proved to the contrary (2) Its fate in the body depends on particle size particles of ½ micron (0 00005 cm) are absorbed and excreted harmlessly in the urine particles larger than 5 micron (0 0005 cm) do not enter the bronchioles and alveoli but are removed by ciliary action and coughing Harmful particles are those between ½ and 5 micron in size (3) Silica produces fibrosis which in the lungs is accompanied by compensatory emphysema (4) Whatever the mechanism silica and tubercle bacilli enhance each other s action Fallon (1937) is probably right when he suggests that both silica and the tubercle bacilli exert their action by disruption of phagocytes

Symptoms of silicosis are due to loss of pulmonary ventilation consequent upon emphysema and fibrosis and occur comparatively late in the disease One man has died as soon as 11 months after the start of exposure but many years often upwards of 20 elapse before emphysema becomes of sufficient degree to be noticed by the patient Silica is irritant to the bronchial tree and a dry non productive cough is common much earlier than dyspnoea Shortness of breath may be of any degree often causing more difficulty in getting to work than when working and in severe cases may be totally disabling A dry irritating cough is present except when acute exacerbation of bronchitis occurs Careful examination shows slight cyanosis clubbing of fingers in about 12 per cent of cases and general wasting Chest signs are often slight and equivocal except when bronchitis is present

During the years 1939–1947 out of 20 782 persons who were certified as being totally or partially disabled from silicosis 19 166 were coal miners The vast majority of disabled miners were employed in the South Wales field (total number of miners in South Wales 65 000) (Meiklejohn 1949) In 1945 out of a total of 5 637 coal miners

certified 5 060 came from South Wales (Capel, 1950) The abnormal incidence of pneumoconiosis including X ray appearances of reticulation amongst miners from South Wales caused special attention to be directed to the type of silicosis liable to occur as the result of exposure to dust from South Wales coal (Fletcher 1948)

Early in the investigation instituted by the Medical Research Council at the request of the Home Office and Ministry of Mines Hart and Aslett (1942) found that the classical radiological description of silicosis was not applicable to many cases They observed with great frequency radiological appearances of a fine network sometimes sharp and lace like in pattern but more often blurred to which they applied the term dust reticulation

Even allowing for the inconsistency of observers and the marked variation between skilled observers the categorisation of X ray films of silicotic chests has proved controversial First class radiological technique is needed Hart and Aslett (1942) used the following classification which is based on empirical observations of films and bears some relation to morbid anatomy

Normal
Reticulation
Nodulation ⎫
Coalescent nodulation ⎫ ⎪
Massive shadows ⎬ Major consolidation ⎬ Consolidation
Multiple fluffy shadows ⎭ ⎭
Local gross lesions of uncertain cause
Lung field equivocal

The lymphatic drainage of the healthy lung is capable of transporting large quantities of dust including silica to the hilar and tracheo bronchial glands Following inhalations of insulting concentrations of dust for example in coal mining local accumulation of dust occurs in small lymphatic nodules particularly at the division of the respiratory bronchioles (Heppleston 1947) Delicate reticular fibres can be demonstrated running through these foci Dust is also present in adjacent alveoli Larger lesions show the same structure but as these become older they are more compact until ultimately obliterated with fibres of collagenous connective tissue Related to these lesions are areas of emphysema of characteristic stellate appearance Gough s method of cutting sections of the whole lung and mounting on paper has shown beyond all possible doubt the relation between coal foci and emphysema—which he terms focal emphysema It is to emphysema that shortness of breath is mainly due This view accounts for the differences between the silicotic lesion (whorled nodulation) where the inhaled dust is nearly all silica (e g Rand miners) and the condition found where the dust is to a large

extent "inert" e g coal mine In the latter silica though in harmful amounts is really a contaminant of carbon

Much dispute has revolved around the aetiology of massive fibrosis Enid Rogers (1946) has claimed in autopsies on patients dying with massive fibrosis to have discovered evidence of tuberculosis in 75 per cent During life tubercle bacilli are recovered from sputum in less than five per cent of cases Fletcher (1948) suggests that depending on conditions not yet understood (but one of which is tuberculous infection) progressive massive fibrosis may (*a*) proceed rapidly with development of recognisable tuberculosis with positive sputum (*b*) show progression with formation of masses of fibrotic tissues from which tubercle bacilli can be cultured after death (*c*) proceed so slowly as to be virtually quiescent in such cases tubercle bacilli cannot be recovered

Hart and Astell s (1942) categorisation of X ray appearances is not inconsistent with the pathology and progress of the diseases even though the exact nature of reticulosis is still to be elucidated Reticulosis is almost entirely confined to miners in the South Wales coal field or to trimmers loading coal from that field and is probably due to the modified effect of silica (see below) accompanied by a gross overloading of the lymphatics with coal dust Seven to nine years after Hart and Astell s first X ray studies Fletcher (1948) reports X ray observations on some of their patients who continued to be exposed to dust these included 158 cases of reticulation six of which have proceeded to nodulation and 34 to progressive massive fibrosis

To explain marked variations in the speed of progression Heffernan (1935) suggested that freshly fractured particles of silica presented unsatisfied valancies at their surfaces In a critical review Wright (1950) has shown that this theory is untenable and that differences in the effect of silica can be explained by variations in surface area of the particles (i e related to particle size)

In 1932 Kettle suggested that iron modified the action of silica During the course of the investigation in South Wales coal field it became apparent to Belt and King (1945) that dust from different seams contained a factor which modified the action of silica King (1945) identified this factor as aluminium In the meantime Denny Robson and Irwin (1937 1939) had employed inhalation of aluminium hydroxide to treat silicotic miners Freshly prepared aluminium hydroxide must be used (Cardner Dworski and Delahant 1944) Published claims for successful relief appear to be proportionate to their author s enthusiasm

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Asbestos. The asbestos fibre is infinitely divisible; it may be 200 microns (1/50 centimetre) or only a few microns in length. The average length is 20 microns (1/500 centimetre). *The difference* between a relatively long fibre of asbestos and fine particulate dust of silica explains the different location of the primary lesion in the lung. Asbestosis starts around the respiratory bronchioles from the region of which phagocytic cells find difficulty in transporting the long fibre. Asbestosis is a diffuse fibrosis affecting the whole lung. Clinically, increasing dyspnoea is the main symptom; a dry cough may be present. Physical signs are absent in the early stages but as infective processes develop rales are heard all over the chest. With the establishment of preventive measures the mortality rate has fallen (in Wyers' (1947) series from 29 per 1,000 to zero in 1940, with a small rise in war years) and with consequent lengthening of life clubbing of fingers may develop. In 1947, 15 persons died from asbestosis. X-ray of the lungs shows a "ground glass" appearance but the chief diagnostic aid is a shaggy appearance of the heart outline. Later the radiological appearances become coarser (Linzbach and Wedler, 1941). On microscopy a fine fibrosis is noticeable throughout the lung, so that the whole lung is "woody". Pleural adhesions are extensive and dense so that difficulty may occur in removing the lungs from the thorax.

Asbestos bodies appear in the sputum of persons exposed to the inhalation of asbestos bodies within about a week. Isolated bodies in small numbers do not indicate the existence of asbestosis; clumps of asbestos bodies are almost indicative of an active process because for such clumps to occur, breaking down of the alveolar wall (often by a suppurative process) must occur (Stewart, Tattersall and Haddow

1932) Careful technique in handling sputum is needed if clumps are to be discovered (Stewart 1934) Gloyne (1929) considers asbestos bodies to be a centre fibre of asbestos coated with iron containing *segmented pigment formed by colloidal action between the fibre and blood proteins*

Asbestosis is often accompanied by an infective process such as bronchiectasis and pulmonary abscess Asbestos does not appear to render the patient liable to tuberculous infection Evidence which is accumulating has almost reached conclusive proportions that a direct causal relation exists between asbestosis and cancer of the lung In 235 autopsies on patients dying from asbestosis, the incidence of pulmonary cancer was 13 2 per cent or more than ten times the incidence observed by post mortem examination in silicotics (1 32 per cent in 6 884 autopsies) (Annual Report Chief Inspector of Factories 1947)

The asbestos industry is small so the number of persons (women nearly equal to men) exposed to asbestos are far fewer than those exposed to silica during the years 1939–1947 103 persons were certified as totally or partially disabled from asbestosis (Meiklejohn 1949) Nevertheless the history of the control of asbestosis should be taken as a lesson in the truth of the need for applying preventive measures as a base for further advances In spite of Montague Murray s (1907) identification of asbestosis and its causation in 1900 for 31 years no legislative action was taken to prevent and reduce the inhalation of asbestos in spite of an expanding industrial use

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Talc For many years Continental and American workers had reported that talc hydrated magnesium silicate occurring in two main physical forms flaky and fibrous caused pneumoconiosis Until the paper by McLaughlin Rogers and Dunham (1949) no certain case of talc pneumoconiosis had occurred in this country This paper should be consulted for full bibliography The essential lesion consists of loosely woven nodules of fibrous tissue often in relation to the respiratory bronchioles Larger nodules are formed by

coalescence "Curious bodies" like asbestos bodies were found close to coalescent lesions and were thought to be due to the chance inhalation of a fibrous form of talc. Symptoms are usually slight but some shortness of breath may be noticed. X-ray *appearances are similar* to asbestosis.

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Aluminium Despite the non toxicity of aluminium hydroxide used for the treatment of silicosis and Hunter Milton Perry and Thompson's (1944) investigation into the health of aluminium grinders aluminium is incriminated from several sources as the cause of pulmonary disease. German workers particularly Jager and Jager (1941) and Goralewski (1943, 1947) insist that *aluminium causes a rapidly fatal pulmonary disease associated with diffuse fibrosis and spontaneous pneumothorax. These reports were confirmed by Frary* (1949) who *noted that the disease occurred only in conditions of bad ventilation (blackout)* and *when aluminium dust was very fine. Shaver and Riddell* (1947) reported a similar illness in conditions of war production among men employed in the manufacture of corondum (aluminium) abrasives from bauxite (consisting of silica and aluminium). Clinically the presenting symptom was often sudden shortness of breath due to spontaneous pneumothorax. A diffuse pulmonary fibrosis of a non nodular type accompanied by gross emphysema and bullæ occurs. In Gardner's opinion (Riddell 1947) it is due to the action of fine particles of silica (Jephcott Johnson and Finlay 1948) modified by aluminium.

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Graphite Dunner (1945) caused much excitement by reporting *five men exposed to the inhalation of graphite* whose chests showed *radiological evidence of reticulation and nodulation.* Later Dunner *and Bagnall* (1946) found that samples of graphite contained from

36 to 10 per cent of free silica One man showed a massive reniform shadow He died three years later aged 67 years and with one other patient was the subject of an investigation by Harding and Oliver (1949) This investigation included a study of the lungs of a man who died after being employed in grinding graphite for 20 years Harding and Oliver believed that the lesions were silicotic in origin and the pneumoconiosis closely resembled that of coal workers

The blocking effects of heavy dust concentrations with secondary action of silica and tuberculous infection cannot be excluded (cf coal miner s pneumoconiosis p 25)

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Benign Pneumoconiosis

Iron Doig and McLaughlin (1936) in spite of American (Sander 1939) efforts to ignore their prior claim first pointed out that the discrete almost pinhead shadows seen in chest X ray films of lungs of electric welders were due to harmless and symptomless deposits of iron oxide Similar shadows can be produced experimentally in rats (Harding Grout and Lloyd Davies 1947) Doig and McLaughlin (1948) have followed some of their original cases and shown that with cessation of exposure the radiological appearances clear

McLaughlin Grout Barrie and Harding (1945) reported siderosis in four silver finishers (who used rouge or crocus two forms of iron oxide) The unexpected death of one man aged 54 years after more than 46 years employment allowed histological demonstration of collections of iron filled phagocytic cells under the pleura along the pulmonary vessels There was complete absence of fibrosis The elastic laminæ of pulmonary arteries and elastic fibrils of the alveolar walls suitably stained showed the deposition of silver

The picture of siderosis may be confused if iron is inhaled simultaneously with silica for example in boiler scalers (Harding Tod and McLaughlin 1944) or in turners and grinders (Bucknell Garrad Jupe McLaughlin and Perry 1946) so that the resulting changes are a combination of siderosis and some form of silicosis

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Tin and Barium A benign pneumoconiosis due to the inhalation of tin oxide giving similar X ray appearances to siderosis has been reported by Pendergrass and Pryde (1948) Barium workers show similar benign lesions (Pancheri 1950)

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Condition with Possible Allergic Basis

Bagassosis, Byssinosis and Pulmonary Mycosis An acute bronchiolitis follows the inhalation of dust of bagasse (sugar cane after extraction of sugar used for insulating boards) (Hunter and Perry 1946) A great many fungi are present in bagasse no evidence of persistence of living fungi can be found in the lungs and though the evidence that allergy plays a part is slight fungi are the probable cause of the irritation If so bagassosis falls into the group including byssinosis (card room workers asthma) farmers lung (Fawcett 1938) caused by the inhalation of fine vegetable dust from mouldy hay broken wind in horses and a febrile condition due to inhalation of low grade stained cotton dust (containing *aerobacter cloacae*) (Neal Schneiter and Caminita 1942) and Thresher s disease (Hoffman 1946 Tornell 1946) The last disease which is of short duration is common through Russia Middle Europe and North South America (Caminita Baum Neal and Schneiter 1947)

Byssinosis mill fever weaver s cough and the acute febrile illness described by Caminita and others may be manifestations of the same phenomenon

Wood dust may cause similar clinical effects

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Pneumonitis

Vanadium manganese and beryllium inhaled in appropriate physical and chemical forms cause an inflammatory lesion of the respiratory tract Cadmium nickel cobalt antimony and osmium may have a similar effect

Vanadium Vanadium occurs in the blood of sea squirts and primitive marine organisms Because of prehistoric deposition of these organisms in oil bearing strata vanadium is obtained by fusion extraction of soot from oil burning liners and residues from oil refineries An important industrial detail is that ganister (silica) linings of furnaces used for fusion and the manufacture of ferro vanadium absorb vanadium These linings are periodically broken down and submitted to the fusion extraction process

Men exposed to vanadium dust (usually in the form of pentoxide V_2O_5) are pallid show the typical green tongue due to staining of the papillæ suffer from green stained sweat and are said to have low blood pressure Vanadium is an acute irritant of the upper respiratory tract attacks of coryza are frequent and bronchitis common Wyers (1946) has reported three cases (one fatal) of pneumonia Wyers states that reticulation may be seen on X ray examination but in the absence of environmental studies this cannot be accepted as due to vanadium in view of the known presence of fine silica dust Sjoberg (1949) states that radiographic changes only occur in cases of pneumonia

Intratracheal injection of vanadium metal vanadium pentoxide and vanadium metavanadate (Lloyd Davies 1949) cause desquamation of the bronchial epithelium and inflammatory changes around the bronchial tree Inflammatory processes do not penetrate into the parenchyma of the lung and resolve within a few days

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WYERS H (1946) Some toxic effects of vanadium pentoxide *Brit J industr Med* 3 177

Manganese In 1939 because of the rise in the incidence of pneumonia in Sauda a small isolated Norwegian village following the opening of a manganese steel works which emitted a pall of smoke over the village Elstad (1939) suspected that manganese increased liability to pneumonia Buttner (1939) noted that Giessen pyrolusite

(manganese dioxide) miners suffered a special class of pneumonia of 17 per 1,000 compared with the local rate of 0·54 per 1,000.

Lloyd Davies (1946) observed a group of men numbering from 40–124 over a period of eight years who were exposed to the inhalation of dust of the dioxide and higher hydroxides of manganese. Acute naso-pharyngeal irritation with epistaxis was noticed by unacclimatised persons entering the works. The average incidence of an acute pulmonary illness usually diagnosed as pneumonia was 26 per 1,000 (range 15–63) compared with a control group of 0·73 per 1,000. Bronchitis was a frequent illness although unsuitable for statistical enumeration because of varying diagnostic standards. Subsequent observation by Lloyd Davies and Harding (1949) showed that pathological organisms were rarely to be found in the naso-pharynx or sputum of acutely ill men. Lloyd Davies (1946) showed that as mice inhaled manganese dioxide it caused a gross mononuclear inflammation of the lung without the intervention of any other factor. Animals so exposed were not more susceptible to pneumococci or streptococci. Lloyd Davies and Harding (1949) by intratracheal injections of suspensions of manganese dioxide into rats produced mononuclear celled consolidation of the lung of characteristic pattern. Soluble manganese salts ($MnCl$ or K_2MnO_4) produced degeneration of the bronchial epithelium and acute superficial inflammatory changes similar to those caused by vanadium. The chance persistence of particles of manganese dioxide caused the production of small granulomatous follicles.

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Beryllium. In 1936 Gelman from Russia and in *1940 Berkovitz and Israel from Germany* reported a *febrile illness with pulmonary* symptoms in *men refining beryllium*. VanOrdstrand, Hughes and Carmody (1943) described an *acute pneumonitis in men* exposed to the *inhalation of fumes produced by* the fluoride method of refining beryl. In a later report VanOrdstrand, Hughes, deNardi and Carmody (1945) noted that nasopharyngitis, tracheitis, bronchitis and pneumonitis may occur.

Hardy and Tabershaw (1946) startled the medical world by reporting an entirely different condition in workers engaged in the manufacture of fluorescent tubes containing beryllium, manganese, zinc phosphors. The onset of symptoms was delayed often for long periods after cessation of exposure. They called the condition delayed chemical

pneumonitis With few exceptions this disease accompanied by severe wasting was progressive and ended in death Diffuse granulomatous changes occurred throughout the lungs and other organs such as liver and spleen Leroy Gardner (1946) renamed the condition pulmonary granulomatosis

Hardy (1951) now prefers the term beryllium poisoning to indicate all types of incriminated beryllium exposure as she regards all clinical syndromes as having a basic pattern She distinguishes —

(1) Acute beryllium poisoning which in a high proportion of exposed and unprotected workers produces dermatitis conjunctivitis and upper respiratory tract irritation and in a smaller number bronchitis and pneumonitis With rest in bed recovery from the pulmonary manifestation is usual

(2) Sub acute beryllium poisoning Whilst losing weight and suffering from some dyspnoea the patient is able to continue some form of work X ray of the chest shows fine bilateral nodularities

(3) Chronic beryllium poisoning is a progressive condition often fatal after a long illness There is a variable latent period *of two weeks to several years following extraordinarily low* exposures to the inhalation of beryllium salts Wasting and dyspnœa are progressive Radiography of the chest shows diffuse bizarre shadows usually nodular or flocculent in character Temporary reversal of these changes and clinical improvement is said to occur under treatment with A C T H Autopsy discloses diffuse granulomatous inflammation having a nodular pattern distinguishable from sarcoidosis with in many cases similar changes in other organs especially liver spleen and lymph glands

Very often a precipitating medical episode e g pregnancy or intercurrent infection appears decisive Hypercalcæmia is a notable feature and a negative nitrogen balance is always present Death occurs in about a fifth of the cases A small asymptomatic group is known to exist Acute and chronic poisoning may co exist Neighbourhood cases proved to have no occupational contact are now known to be due to atmospheric contamination occurring around factories

Evidence is accumulating to show that beryllium compounds for example beryllium phosphate of large particle size do not cause poisoning In an extensive inhalation experiment using several species of animals Hall and others (1950) showed that beryllium oxide specially calcined at 400°C produced an acute pneumonitis and this was related to the small particle size Other samples of beryllium with larger particle size failed to produce injury

Table II is reproduced from Hardy's (1951) paper to show the source and number of known cases in the U.S. of chronic beryllium poisoning.

TABLE II

Number of Known Cases of Beryllium Poisoning in U.S. from 1938 (Hardy, 1951)

Process	Clinical Designation	
	Acute	*Chronic*
Extraction of Be from ore	300+	11
Machining Be	10	4
Fluor. powder mfg	7	3
Fluor. lamp mfg	5+	110+
Fluor. sign tubing mfg	—	13
Be alloy mfg	—	10+
Neighbourhood cases	—	9
Fluor. lamp salvage	—	4
Research work	—	6+
Radio tube mfg	—	6
Ceramics	—	3
Silica crystal mfg	—	2
Mining and handling beryl ore	—	—

Note.—Only one case of chronic beryllium poisoning has been reported in the English literature (Agate, 1948) and it is doubtful *if more than one or two others are known.*

To speak of "solubility" of inhaled particles is misleading, as a solution implies even dispersion throughout a solvent. A point may be reached when there is little difference between molecular solutions and suspension of very minute particles. Nevertheless the effect of inhaled dust in the lung is largely determined by particle size which determines the speed of solution (using the term loosely to mean absorption of particles into body fluids) or conversely the time of persistence of particles.

As referred to on page 27, Wright (1950) has produced much circumstantial evidence to support the suggestion that the effect of silica is determined by particle size and the area presented to body tissues. Vanadium, manganese and beryllium produce a progressive series of changes from acute oedema and transitory acute inflammation to persistent chronic granulomatous inflammation, which changes are related to the "solubility" of the salt. Soluble salts of manganese produce the same effect as vanadium salts (which are all highly soluble) whereas the chance persistence of a relatively insoluble particle such as manganese dioxide in the lungs of rats produces granulomatous changes. Policard (1948, 1950) and Lloyd Davies and Harding (1950) have produced granulomata in the lungs of experimental animals by intratracheal injections of suspensions of beryllium oxide. Nevertheless this theory only explains the occurrence of histological

effects in a progressive series it does not explain how the cellular effects are produced As Hardy (1951) suggests beryllium may well cause its effect by upsetting the magnesium metabolism or even replace magnesium with consequent inhibition of enzyme systems

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TOXICOLOGY

Cyanide Poisoning

War time research disclosed that the administration of nitrites by forming methæmoglobin in the blood protected against cyanide poisoning Evidence exists which suggests that methæmoglobin competes with the respiratory pigment ferricytochrome oxidase for the cyanide ion Treatment based on these observations has proved successful in cases of severe cyanide poisoning

(1) Inhalations of amyl nitrite (which can be given by unskilled persons pending medical aid)

(2) Intravenous injection (2 5–5ml per minute) of sodium nitrite (0 3 grams in 10ml sterile distilled water)

(3) Slow intravenous injection of sodium thiosulphate (25 grams in 50 ml sterile distilled water) followed by

Removal to fresh air artificial respiration and oxygen therapy must of course be undertaken as indicated

Insecticides

Horticultural practice now includes the use of powerful insecticides which are also powerful poisons to man

Organic phosphorus insecticides (Hexaethyl tetraphosphate (H E P T) tetraethyl pyrophosphate (T E P P) diethyl para nitrophenolpyrophosphate (parathion) Octa methyl pyrophosphoramide (O M P A) is too toxic to use on crops intended for food

These substances resemble di isopropyl fluorophosphonate (D F P) used in dilutions of 0 05 to 0 2 per cent in arachis oil to treat glaucoma and inhibit cholinesterase systems Persons affected include workers employed in spraying and picking crops packers entomologists and aeroplane pilots (flying aircraft used for spraying) Early symptoms included dizziness and visual failure (an aeroplane crash is thought to have occurred from this cause) Other symptoms are often delayed and do not occur until after the day s work is over Apprehension dizziness nausea and vomiting abdominal cramp diarrhoea and muscular twitching are usual Constriction of the pupil is found in all moderate and severe cases Later pulmonary oedema supervenes and is followed by deep coma and convulsions

Symptoms due to over stimulation of the autonomic nervous system will respond to the intravenous injection of atropine (gr 1/60–1/30) repeated hourly until the pupils dilate Combination of cholinesterase with T E P P and parathion is reversible after several hours For this reason the prompt and adequate administration of atropine is important (Bidstrup 1950) Toxic effects on the central nervous system apparently peculiar to parathion also respond to atropine Paralysis of the neuro muscular junction produced by all substances does not respond to atropine Respiratory paralysis may be of sudden onset without warning continuous watch needs to be kept on a patient poisoned with these substances Means of prolonged artificial respiration should be immediately to hand

Absorption takes place through the lungs by inhalation of dust or spray but parathion being lipoid soluble may be absorbed through the skin and conjunctiva The skin should be washed with soap and water containing a mild alkali as parathion hydrolyses more rapidly in the presence of alkali Poisoning is cumulative owing to slow rate of recovery of cholinesterase Strict enforcement of protective measures including total enclosure of tractor drivers and wearing of protective clothing is needed Fruit and vegetables should not be gathered or eaten within six weeks of spraying with parathion

Dinitro orthocresol (D N O C) Absorption of D N O C either during its manufacture or during fruit spraying causes increase of the basal metabolic rate The chief symptoms are thirst increased respiration with very rapid pulse cyanosis and hyperpyrexia which may result in death in a few hours Absorption is usually by fumes through the lungs (horticultural spraying is more effective on a warm still day) but skin absorption may occur

Organic mercury compounds (methyl mercury iodide phenyl mercuric nitrate ethyl mercuric acetate and di ethyl mercury)

Besides causing dermatitis and skin burns organic compounds of mercury used to protect wheat and other cereal seeds from fungal infections have caused the deaths of several persons Toxicity to man and to fungi appears to decrease with increasing weight of the hydro carbon group Methyl mercuric iodide is too toxic to be manufactured Hunter Bomford and Russell (1940) have reported four cases of poisoning by methyl mercuric iodide characterised by ataxia dysarthria and gross contraction of the visual fields Memory and intelligence were unaffected The usual symptoms of mercury poisoning saliva tion stomatitis and erethism were absent Animal experiments confirmed that widespread and intense degeneration of sensory paths of the nervous system occur Peripheral paths and posterior spinal roots were affected first to be followed by degeneration of the posterior columns of the cord and granular layer of the middle cerebellum

Two girls died in Canada after having worked for six months in a room separated by a cardboard partition from a store containing 20 000 pounds of di ethyl mercury (Air concentration was 2 7 mg of mercury per cubic foot of air) (Hill 1943)

Organic mercury compounds must be handled under conditions of exhaust ventilation The use of respirators and protective clothing is inadequate

Once again poisoning by organic mercury compounds might have been anticipated and so avoided if care had been taken to consult the literature In 1863 Frankland and Duppa reported two cases of fatal poisoning from di methyl mercury after brief contact Both were laboratory technicians one of whom had handled the substance for three months and one for two weeks only

R D X Cyclonite (Trimethylenetrinitroamine) Inhalation of R D X powder for a few months results in repeated epileptiform fits according to German experience during the war A period of about two days insomnia and restlessness precedes the sudden onset of a fit Fits are followed by deep coma lasting several hours and weakness nausea and headache lasting several days Recovery follows removal from exposure

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RADIATION

Radiations of practical importance in industry are —

(1) Infra red rays Wave length about 8 000–12 000 A U

(2) Ultra violet rays Wave length 100–4 000 A U

The wave length of the visible spectrum is 8 000 A U (red) to 4 000 A U (violet)

(3) Ionising radiations (radioactive emanations and X rays)

Infra red Rays

Cataract The romance of the discovery by Alfred Greenwood the partially blind secretary of the Glass Bottle Makers of Yorkshire United Trade Protection Society of glass bottle finishers cataract is told in dramatic form by Legge (1934) Subsequently in 1891 Robinson (1903) of Sunderland identified the cataract as of post cortical type The formation of a cataract is due to over heating of the eye and consequent interference with the metabolism of the lens

All persons exposed to the heat radiations particularly puddlers and strip rolling mill hands are liable to similar cataract

The insidious onset over many years makes the adoption of protective measures difficult Heat glare should be avoided or minimised and spectacles with Crookes lens worn Prior to the National Insurance (Industrial Injuries) Act 1946 compensation was payable for glass blowers cataract for four months only

In the Black Country where chains are still made by hand chain makers *develop a peculiar exfoliation of the lamellæ of the anterior capsule* The furnace is on the left of the worker and the left cataract is nearly always more advanced than the right (Moore 1948)

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LEGGE T (1934) Industrial maladies Oxford p 25

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Ultra violet Rays

Arc Flash The great increase of welding particularly electric makes *ultra violet radiation a common hazard* No conclusive evidence exists that U V L produces permanent changes in the eye or in the retina (Kuhn 1944) The effects of U V L are confined to the cornea and conjunctiva A very painful condition inappropriately known as arc flash characterised by weeping photophobia and blepharospasm, results from incautious exposure to U V L A welder has to use protective goggles or screen to see his work arc flash which is the cumulative effect of U V L is usually contracted from the arcs of neighbouring workers in the intervals between work when goggles are removed Welding booths should be efficiently screened Ordinary

spectacles will protect casual visitors for a few minutes At 50 feet Drinker (1944) calculates an exposure of 21 3 minutes is required to contract arc flash

Most relief is obtained by cool air and sufferers often sit as passengers with their heads out of the window in motor cars Goggles and screens with glass of B S I specification to suit the particular form of welding should be used

Skin Cancer Ryle and Russell (1947) in England and Hueper (1942) in U S A have collected evidence which strongly suggests that pigment and keratotic changes consequent on continuous exposure to sun light may be accompanied after many years by epithelioma or rodent ulcers Trauma may be an associated cause

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Ionising Radiations

Physical Concepts—An atom consists of a positively charged nucleus containing the main mass of the structure and surrounded by a number of negatively charged electrons The nucleus consists of protons equal in number to the satellite electrons and carrying an equivalent but opposite charge so that the atom is electrically neutral The number of protons or electrons is called the atomic number of the element

The simplest element hydrogen has one proton and one electron and the next simplest helium has two protons and two electrons On this basis helium would be expected to have double the atomic weight of hydrogen In fact helium is four times as heavy as hydrogen which is explained by the fact that the nucleus contains two uncharged bodies called neutrons having nearly the same mass as protons

The number of electrons and protons in an atom determines the chemical properties but the number of neutrons may vary without changing the chemical form although a change in atomic weight will result Atoms of the same number but with differing atomic weights are known as isotopes Thus carbon with atomic number 6 and atomic weight 12 consists of six electrons six protons and six neutrons but a rare form of carbon exists containing 7 neutrons The two forms may be written C_6^{1} and C_6^{13} respectively There are some 890 isotopes of the 96 elements known of which about 300 are stable and the remainder unstable and radioactive

Radioactive heavy atoms are continually breaking down α particles consisting of two protons and two neutrons the helium nucleus breaking away

Some lighter atoms may break down because the nucleus contains too many neutrons In order to achieve stability a neutron changes

into a proton When this happens *an electron or β particle is given off* A gamma ray may be released during this process

The essence of an atomic pile is the bombardment of fissionable atoms by neutrons to produce radioactive substances *More neutrons* (and other forms of radiation) are by products

There are then four types of radiation

α particles comprising high speed (12 000–18 000 miles per second) helium nuclei built up by grouping of two protons and two neutrons capable of penetrating only a few centimetres of air The depth of penetration into tissues is 50 microns Though α particles produce intense ionisation they are of little practical importance because of *their short path*

β particles comprising high speed electrons ejected from an atom with a speed 30 90 per cent that of light as their mass is 1/7000 *that of α particles they have more penetrating power though they* are stopped by a few millimetres of solid matter including body tissues Their effect is largely confined to the skin but is variable *because when stopped they scatter easily They are identical in* nature with planetary electrons which whirl round the nucleus of an atom

γ-rays are electromagnetic waves *indistinguishable in their effect γ rays* (less than 0 01 A U) and high voltage (hard) X rays (0 01–1 0 A U) have great power of penetration

Neutrons which are uncharged particles almost equal in mass to a proton are unaffected by charged nuclei or electrons and have a greater chance in passage through matter of hitting a nucleus than a proton or α particle Their powers of penetration are great

γ rays X rays and neutrons being uncharged electrically cause *ionisation indirectly*

Biological Effects of Radioactivity The biological effect of radioactivity and X rays is due to ionisation of matter through which radiations pass Cell proteins are ionised but the effects are most easily demonstrated by breaking of chromosomes at the point of passage of rays or by disintegration of the nucleus Besides loss of *function of the affected cells toxic products from protein breakdown* are released causing fever and shock like toxaemia

Ionising radiations act selectively on tissue undergoing mitosis e g germinal epithelium hæmopoietic tissue and neoplastic *tissue*

The most important effects are —

(1) *Haemopoietic system* Changes in the hæmopoietic system include diminution in the number of circulating lymphocytes granulocytes platelets and red cells usually developing in *that order Lymphocytes* are affected *in a few* hours but after diminishing for four to five days begin to increase in number Clotting time is increased and plasma proteins diminish (causing a rise of the sedimentation rate which usually takes a week *to develop)* Ultimately the bone marrow becomes aplastic

(2) *Germinal epithelium* Testes are more easily damaged than ovaries but it is doubtful if permanent sterility can be produced by one dose of radiation which is not lethal Repetitive doses of small amounts may cause permanent sterility Genetic effects are discussed below

(3) *Gastro-intestinal system* Mucous membranes become injected œdematous and ulcerated Symptoms are nausea vomiting and later bloody watery diarrhœa

(4) *Skin* Single large doses cause erythema Repeated short exposures as in radiologists not employing protective clothing after a varying interval from a few weeks to several years depending on intensity of exposure cause the skin to become atrophic The skin is roughened cracked and of thin texture over the knuckles it becomes swollen and stiff Capillary hæmorrhages usually occur Nutrition of the nails is affected causing splitting and striation Epilation is usual Ulceration of the skin generally occurs and may involve deep structure and progress to gangrene The condition is excessively painful Amputation may be necessary Malignant changes are common in old standing dermatitis

(5) *Blood vessels* Increased permeability œdema of vessel walls thrombosis and rupture cause secondary symptoms

(6) *Rarifying osteitis* Radioactive substances absorbed into the body are stored in bone Internal radiation from these stores besides bombarding hæmopoietic tissues may after many years produce a rarifying osteitis similar to phossy jaw The first sign may be a fracture Bone neoplasms may occur

(7) *Tumour formation* produced by ionising rays may occur in the skin blood forming tissues lung and digestive tract as well as in bone Tumours do not necessarily occur at the site of radiation but may appear remotely due presumably to a constitutional effect Cancer of the lungs in Schneeberg and Joachimsthal miners engaged in getting cobalt arsenide ore is due to radioactivity Though arsenic and cobalt may play a part sufficient radioactivity is present in the mines to cause pulmonary malignancy (Evans 1949)

(8) Post cortical cataract has been reported in physicists exposed to neutron beams from cyclotrons

Genetic effects The development of atomic energy plants and the possible effect of atomic bombs render the consequence of mutations of great importance Ninety per cent of mutations are harmful even if produced naturally Radiation will only produce mutations which can be produced by other means but it induces an increased mutation

rate Much of the experimental work on mutations has been on *Drosophila* To what extent still births and malformations will occur in the human race is not clear Evidence that an increase of congenital malformations has occurred in Hiroshima or Nagasaki since atomic bombs were exploded is slight From the point of view of the race, the proportion of the population irradiated even at low intensity is the crucial factor In any case genetic effects may not be apparent for many generations owing to the possible development of recessive changes *Hamilton and Hardy (1949)* believe X ray diagnostic procedures to be so frequent in the life of an adult at any rate in the U S A as to constitute a danger They point out that an X ray machine delivers 1 5 to 3r to the subject of a chest X ray and 25 to 30r to a patient undergoing gastro intestinal fluoroscopy

The maximum ' permitted dose of radiation has been reduced from 0 1r to 0 02r a day by the International Commission on X ray and Radium Protection to guard against genetic injuries The body is normally exposed to 0 1r per year from natural sources (cosmic rays gamma rays and minute amounts of radioactive potassium and carbon) The normal amount of radioactivity in the body is below 1 millicurie

Whether dangerous emanations of the X ray and radioactive variety are produced by Röntgen tubes radium and similar radioactive substances or by atomic explosion matters little The main difference is the intensity of production which influences the likelihood of damaging effects and of casualties

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HAMILTON A and HARDY H L (1949) Industrial toxicology 2nd edit New York p 455

Atomic Fission

Atomic explosions in bombs bursting in air may cause lethal or serious effects on life for 600–800 yards from neutrons and for 1 500–2 000 yards from radiation Even so the most widespread effect would be by infra red rays (mild burns up to 4 000 yards radius) or by blast

Gamma radiation sickness was well illustrated in Japan after atomic bombs had been burst over Hiroshima and Nagasaki Apparently doses of 600r are lethal 400r cause a profound illness of delayed onset with 50 per cent death rate Symptoms include vomiting diarrhoea and inflammation of the mouth and throat fever and rapid wasting White cell counts fall to 2 000 cells per c c Death takes place from infection and toxæmia Doses of 100–400r cause similar but less profound illness lasting about three weeks

Industrial Use of X rays or Radioactive Substances

In industry apart from Government atomic energy plants, the main hazards from radioactivity result from the use of X rays to examine industrial products (e g, castings cables, eggs and even golf balls), in laboratories the occasional use of radium radon or radioactive isotopes, and the handling and use of luminous paints Radium and more recently polonium is being used to produce α particles to remove static electricity by intense ionisation of the air where a risk of explo sion exists X ray shoe fitting machines many of which are badly screened may expose salesmen to a daily dose of 1r or more which is many times more than the International permitted dose and five times the accepted British tolerance dose of 0 2r

Luminising Martland (1931) records the tragic deaths of a number of girls employed in the U S A between 1917 and 1924 in painting luminous dials They were allowed to point brushes by moistening with their lips and death followed after varying intervals from blood dyscrasias neoplasms and rarifying osteitis Strict *precautions were therefore enforced in Great Britain in World War II* and as a result no harm occurred from luminising compounds (Annual Report Chief Inspector of Factories 1947) This is particularly creditable as very large quantities of instruments with luminous dials were produced Besides the mixing and storage of paint the painting of dials and the storage of the finished instruments in bulk also con stitute hazards

For non civilian use luminising powders consist of zinc sulphide with the addition of 70 grammes of radium or mesothorium per gram Only a small amount is used dry before use the greater part is con verted into a paste Browning (1949) noted that the characteristic deviation of the blood from normal shown by luminisers was a relative lymphocytosis with moderately high total white cell count together with the presence of immature cells In seven per cent of cases these were immature mononuclear cells

Potential exposure consists of (1) irradiation by α β particles and γ rays (2) inhalation of radon (3) inhalation of radioactive dust (4) ingestion of luminous compound from contamination of the fingers

Luminising should be done in individual booths constructed of easily washed and impervious material on a clean impervious bench, with glass screening between the work and the operator and adequate exhaust ventilation Ingestion must be prevented by repeated warn ings and scrupulous hygiene Food tobacco cosmetics must not be introduced into the work room Washing and cloakroom facilities must be of the highest standard Operators must wear clean protec tive clothing fastening round wrist and neck The nose and mouth should be covered by a mask The hair must be totally enclosed

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Whether dangerous emanations of the X-ray and radioactive variety are produced by Röntgen tubes, radium and similar radioactive substances or by atomic explosion matters little. The main difference is the intensity of production which influences the likelihood of damaging effects and of casualties.

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HAMILTON, A., and HARDY, H. L. (1949) Industrial toxicology, 2nd edit., New York, p. 4[illegible]5.

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Health Physics

Besides the medical control measures described on page 45 the monitoring by physicists of persons and plants handling radioactive substances is essential Gaseous and fluid effluents need strict checks For the detection of small amounts of radioactivity the Geiger counter is employed but small pocket electroscopes are being developed Estimation of the radioactivity present in breath urine sputum and nasal mucus of exposed workers may need to be undertaken regularly In the U S A 10^{12} curie per litre is considered the maximum amount of radon which can be permitted in the exhaled breath of workers exposed to radium In England the similar accepted figure is 10^{11} curie Wounds contaminated with radioactive substances should be excised

The amount of radioactivity in the body may need to be measured (Jones and Day 1945) The amount of radioactive substances that can be tolerated by the body depends on the number of disintegrations per minute For example the body can tolerate 1 microgram of plutonium which has 14 disintegrations per minute Besides the rate of disintegrations the site of storage and fate of disintegration products needs to be known Janet Vaughan (1950) points out that radio strontium is stored in the growing ends of bone but yttrium to which it disintegrates is stored throughout the skeleton

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Impervious aprons should be worn together with gloves when paint is mixed or washing of benches is done. Solid applicators (not brushes or pens) must be used. Not more than a small quantity (less than 1 gram) of powder should be mixed into a paint at a time. Unspillable screened containers should be used. Benches and floors should be washed daily.

Nevertheless in spite of every care small splashes are bound to occur and these dry into dust which can be demonstrated by means of U V I illumination. In Browning's series (1949) such blood changes as did occur were due to "internal" radiation from the inhalation of this small amount of dust. For this reason adequate periods of non exposure must be enforced. The Factories (Luminising) Special Regulations 1947 No 865 besides making provision for precautions outlined above require that no person should work for more than 48 hours a week for more than 12 months without an interval of three months from exposure. Periodic medical examinations (which should include periodic blood counts taking care that a normal is established first for each patient and the hæmatological technique is good) are prescribed together with a periodic exposure of test X ray films (to be obtained from and sent to the National Physical Laboratory).

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Isotopes (See also Chapter IX)

The development of atomic energy piles has made possible the manufacture in large quantities of radioactive isotopes. At least one radioactive isotope and sometimes more of every known chemical element (see page 41) has been produced.

When used in tracer experiments radiation will prove harmless to the operator if it does not kill the experimental animal but the effect of cumulative doses must be considered. The help of skilled physicists is needed to ensure that external radiation is kept within tolerable limits. C^{14} which is often met in experimental work has been detected in the bones of animals four months after administration (Bloom 1947). Though the radiation from C^{14} is weak it must be used with caution because of its long half life of 4 700 years. Radioactive Iodine (I^{131}) has been used in the treatment of hyperthyroidism (*Chapman and Evans* 1946) and malignant growth of the thyroid (Pochin 1950). In 22 cases no permanent harmful effects were seen but transitionary symptoms of X ray sickness (nausea vomiting fever) were experienced. P^{32} has been tried experimentally in leukaemia, Hodgkin's disease and polycythemia vera with varying success.

opening) through the pleuro peritoneal hiatus (foramen of Bockdalek) or elsewhere in the diaphragm either as a result of the congenital absence of a portion of the diaphragm or following direct or indirect trauma In clinical practice the important group consists of herniation through the œsophageal hiatus and it is becoming increasingly clear that this is a common condition frequently overlooked in the past because a special radiological technique is necessary for its demonstration There is a protean clinical picture which includes dyspepsia of all degrees ranging from heart burn or wind in the stomach to intense boring pain related to meals dysphagia pain simulating angina but not related to exercise obscure cases of anæmia and unexplained haematemesis The common classification is as follows —

(1) The congenitally short œsophagus
(2) Paraœsophageal hiatal hernia The lower œsophagus remains in the normal position and a portion of the cardiac end of the stomach herniates through the hiatus alongside the œsophagus
(3) The œsophago gastric hernia Both the lower end of the œsophagus and a portion of the cardiac end of the stomach prolapses through the œsophageal opening

The congenitally short œsophagus undoubtedly occurs but is extremely rare and it is now recognised that in most cases of short œsophagus in adults the shortening is secondary to œsophagitis and ulceration which has occurred from reflux of gastric content as a result of incompetence of the œsophageal hiatus

The studies of Allison have provided a better understanding of the development of hiatal hernias At the œsophago gastric junction there is no thickening of the circular fibres of the œsophagus to form a sphincter but the canal takes a bend forward to the left and this bend is lassoed and maintained by the right crus of the diaphragm which hitches it down to the lumbar spine The œsophageal hiatus is formed by a split in the muscle fibres in the right crus In front the œsophagus is supported by a sling of muscle fibres continuous on each side with the perpendicular fibres of the crus and decussating with one another to form a stoutly re enforced raphé Behind there is less support for it is here that the crus splits to form the hiatus When the right crus of the diaphragm contracts its action on the cardia is two fold First it compresses the walls of the œsophagus from side to side and secondly it pulls down and increases the angulation of the œsophagus Allison considers that the weak area is behind the œsophagus where increasing pressure is felt along the grain causing splitting of fibres to increase the size of the opening He considers that this forms the key to the problem of surgical repair From his

CHAPTER III

GASTRO-INTESTINAL DISORDERS INCLUDING LIVER DISEASES

by

F AVERY JONES

Dysphagia Hiatus hernia Achalasia Plummer Vinson syndrome Spontaneous perforation of oesophagus Peptic ulcer Effects of partial gastrectomy Treatment of chronic hepatitis Liver function tests Liver biopsy Nutrition and liver disease Virus hepatitis Ulcerative colitis Megacolon

PROGRESS in gastroenterology in recent years has been mainly through increased accuracy of diagnosis keener appreciation of the influence of emotional factors on the alimentary canal and a more rational approach to treatment by diet Environmental factors in peptic ulcer have been carefully studied but there are no real advances in treatment The mortality for partial gastrectomy has declined and many gastric cripples have returned to full work but a small price has to be paid in troublesome post gastrectomy syndromes In liver disease the pathology of acute hepatitis has been firmly established and there have been valuable advances in the medical treatment of liver damage and in the surgical management of portal hypertension

DYSPHAGIA

Hiatus Hernia

Herniation of the stomach through the diaphragm most commonly occurs through the oesophageal hiatus but herniation may also take place through the foramen of Morgagni (the anterior substernal

again Her husband says that for belching she takes the first prize Four years ago she was thought to have cholecystitis but removal of either a normal or abnormal gall bladder did not cure her Radiography of her stomach and duodenum shows no evidence of ulcer She has tried all the advertised stomach medicines with only temporary relief and has finally been told that the nerves of her stomach have been upset by the change of life This story with minor variations occurs often enough in the hospital outpatient department to deserve more notice and better treatment '

It is these patients who may develop a peptic ulcer of the œsophagus but it will be seen that the shortening is secondary to the hernia and not the primary cause of the condition as was previously thought With the development of ulceration the symptoms become more insistent and were beautifully described by Dick and Hurst (1942)

Pain which is burning or smarting and often described by the patient as heartburn is almost invariably present It is felt whilst actually eating or drinking At first it occurs only when hard food such as tough meat a crust or a piece of apple is insufficiently chewed and with chemical and thermal irritants such as strong alcoholic or very salty drinks vinegar hot soup tea or coffee or very cold water or ices Later it occurs with every meal but bland fluids such as milk can always be drunk without discomfort The pain at first lasts for only a few minutes and is at once relieved by alkalies but later it is more prolonged and less completely relieved It may amount to no more than discomfort but it is often so severe that the patient becomes frightened to eat and consequently rapidly loses weight and strength Pain is also felt an hour or two after meals if the patient bends forward as in gardening or picking something up from the floor or if he lifts a heavy weight He soon learns to avoid such exciting causes one of our patients had garden tools with very long handles specially made for her so as to avoid bending In a large proportion of cases the pain returns within a few minutes of lying down at night and also on lying down during the day In some cases this symptom precedes the pain associated with eating After a late dinner the pain may waken the patient at one or two a m instead of being felt directly he goes to bed The intense burning pain behind the sternum is then often accompanied by regurgitation of very acid clear fluid which he spits from his mouth in striking contrast with the alkaline waterbrash which frequently accompanies the epigastric or right sided night pain of duodenal ulcer Sitting or standing up arching the back and stretching the arms upward may bring

studies he concludes that herniæ are of two main varieties the para œsophageal or rolling and the sliding, each group giving rise to different symptoms and having different prognoses. In some individuals there is a hernial sac of the peritoneum in front of the œsophagus which may remain empty during the whole of a patient's life. Alternatively, a part of the anterior surface of the stomach may project into it. As long as the ligaments of the cardia remain strong the hernial sac can only fill by rolling up of the anterior wall of the stomach and indeed in extreme degrees the stomach is found upside down in the mediastinum within a peritoneal sac. As the œsophagus still enters the stomach at an acute angle, there is no regurgitation of gastric content into the œsophagus and therefore no œsophagitis. These patients complain of fullness after meals, wind round the heart, palpitation and shortness of breath and may have secondary anæmia from constant small loss of blood or episodes of severe pain from volvulus of the stomach.

With the second type of hiatus hernia, the sliding hernia, there is no existing hernial sac but a general weakening of the muscles and ligaments at the cardia and what amounts to a direct hernia may result. The cardia may slide up into the mediastinum, the acute angle between the œsophagus and stomach disappears and the stomach hangs vertically from the œsophagus. The œsophagus being a highly elastic organ coils and appears considerably shorter. These patients readily regurgitate gastric juice into the gullet and develop œsophagitis which may lead to ulceration and further shortening by scarring. Allison (1951) presents a very graphic composite picture of patients with œsophagitis from sliding hernia.

A woman of 59 years of age complains that for six years she has suffered from intense burning pain behind the lower part of the sternum which rises up towards or even into the neck. It may spread into the jaw, the ear or the hard palate or radiate through to the back between the shoulder blades or down the arm. It comes on especially when she exerts herself stooping forward as in washing the floor, bending over the wash tub, poking the fire or fastening her shoes. It wakes her in the middle of the night, especially if she is sleeping on her back or her right side, and she seeks relief from what she describes as an agonising pain by sitting upright and taking a few sips of water, milk or alkaline mixture. She says that her throat usually feels dry and burning. When she swallows she may be conscious of the passage of food down the gullet; it may cause a feeling of soreness and may sometimes lodge towards the lower end of the sternum causing pain which is immediately relieved as the bolus passes into the stomach. If she bends forward after a meal food or sour fluid rises into her throat and has to be swallowed

Achalasia

The term cardiospasm is misleading for there is no morbid anatomical evidence of spasm being the cause of the delay in emptying of the œsophagus and the present view favours a failure of relaxation of the abdominal œsophagus and Templeton (1944) describes a failure of peristaltic waves to reach the cardia in this condition Three forms of œsophageal contractions may be observed in normal people — 1 The primary peristaltic wave initiated by swallowing It begins with contraction of the pharynx and in most instances flows in an uninterrupted manner to the cardia 2 The secondary peristaltic wave usually arises at the level of the aortic arch and is initiated by distension of the œsophagus It is sometimes observed in individuals in whom the primary wave fails to carry the bolus through the œsophagus Both the primary and secondary waves are preceded by a wave of inhibition which causes the œsophageal wall to relax ahead of the on coming wave of contraction 3 The tertiary waves are both segmental and tonic in character They are rarely seen in young people but are encountered frequently in older individuals In the portion of the œsophagus below the level of the arch of the aorta simultaneous irregular contractions of the distended œsophagus may be seen giving a peculiar irregular serrated appearance they are usually accompanied by a tonic phase which diffusely narrows the lumen

In achalasia the muscular action differs from normal The primary wave instead of proceeding the entire length of the œsophagus as it does normally ceases at about the level of the suprasternal notch or even higher The portion of the œsophagus over which the wave passed remains contracted for a brief period and when it relaxes the contents of the œsophagus flow upwards but are prevented from entering the pharynx by the contracted crico pharyngeal muscle No secondary waves are observed Shallow purposeless segmental contractions constantly appear and disappear at different levels of the œsophagus producing an undulating effect but are not sufficiently deep to move the bolus along This muscular activity which simulates the local or tertiary contractions is best seen in patients with slight degrees of dilatation These undulating movements are associated with a generalised tonic contraction which narrows the œsophagus and barium passes into the stomach as the *cricopharyngeus remains* tightly contracted

There is thus a definite pattern of abnormal muscular contraction in achalasia The peristaltic wave initiated by swallowing passes only through the upper or striated muscular portion of the œsophagus and does not continue into the lower or smooth muscular portion This section is in a state of constant segmental contractions which do

relief, which is also brought about while drinking water Some patients discover for themselves that the night pain can be prevented by keeping the shoulders raised on three or four pillows The pain is situated in the middle line deeply beneath the lower end of the sternum *corresponding with considerable accuracy to the actual position of the ulcer* Sometimes it passes through to the back between the shoulder blades less frequently upwards to the left side of the neck and jaw and occasionally down the *left arm* "

Peptic œsophagitis from hiatal incompetence may sometimes develop during pregnancy Rennie, Land and Park (1949) described five cases and it is probably an important cause of severe heartburn *in the last three months of pregnancy and of hæmatemesis occurring* at this time Large ovarian cysts may similarly produce symptoms of diaphragmatic hernia Oesophagitis may also follow an abdominal operation such as that for perforated ulcer This is a rare complication *but presumably due to a reflux at a time when the patient was collapsed* Dysphagia may follow shortly after operation and a smooth narrowing of the lower œsophagus will be found Spontaneous rupture of the œsophagus is a particular hazard if these patients have pyloric stenosis *and vomit repeatedly, and the condition should be regarded as an* additional indication for partial gastrectomy

Hæmatemesis may occur either from superficial or from chronic ulceration or from associated ulcer in the stomach or duodenum *Chronic anæmia from blood loss is not uncommon and this diagnosis* must be considered in the investigation of cases of obscure anæmia and of all cases of hæmatemesis in whom no ulcer can be found in the stomach or duodenum Quite large hiatal hernias without symptoms *may be discovered accidentally and may even be seen in a plain X ray* of the chest

The symptoms of many patients can be controlled by simple medical measures such as diet small meals reduction of obesity sleeping *propped up at night by pillows raising of the bed head six inches* or taking alkali last thing at night However when symptoms are severe surgical repair through the chest should be considered and the patient referred to a thoracic surgeon

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dilator is inserted over the stilette The constricted part of the œsophagus must be in the centre of the Negus bag otherwise the bag slips either up or down producing no dilatation of the constriction It is advisable to inflate the bag with 20—40 ml of water at at least three different levels making certain that the bag is gripped by the constriction Wooler treated 38 of his cases with Negus hydrostatic dilator Thirty three were followed up six have been improved and 27 are *entirely free from symptoms If this method fails* the next line of treatment recommended is Heller s operation The œsophageal muscle is incised longitudinally in the region of the constriction in the same way as in Rammstedt s operation for hypertrophic pyloric stenosis of infants The operation for anastomosing the stomach and œsophagus has proved unsatisfactory as peptic ulceration may develop in the œsophagus

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Dysphagia with Iron Deficiency Anæmia and Vitamin B Complex Deficiency in Women

The salient features of this syndrome are hypochromic anæmia cracks at the angle of the mouth (cheilosis) smooth tongue hollow brittle nails (koilonychia) There is usually achlorhydria or hypo chlorhydria Dysphagia may be a troublesome symptom in some cases Although it can occur in men particularly after gastro duodenal operations it is essentially a disease affecting women during the reproductive period of life The common factor appears to be an iron deficiency state often due to a poor diet and aggravated by increased blood loss The whole syndrome will improve slowly with the administration of iron e g ferrous sulphate 3 grains t d s The koilonychia (Glazebrook 1944) and dysphagia (Waldenstrom and Kjellberg 1939) can occur without anæmia but associated with low serum iron levels and the term sideropenic dysphagia may be used The angular stomatitis or cheilosis and also the dysphagia will respond *very quickly to Vitamin B complex and has been considered to be* particularly a manifestation of riboflavin deficiency The curative effect of riboflavin on the angular stomatitis and also on the dysphagia and koilonychia (Lundh and Geill 1942) has been recorded in the *so called* Plummer Vinson *syndrome Rapid* effect can be obtained by the injection of 5 milligrams of riboflavin twice daily It is possible that iron deficiency may condition disturbance in the metabolism of

not pass the bolus down the œsophagus Templeton considers that these latter contractions have been previously mistaken for peristaltic waves The achalasia or failure to relax of the lower end of the œsophagus is due to the failure of a normal peristaltic wave to reach the cardia and the primary defect is therefore in the smooth muscle portion of the œsophagus

Achalasia may occur at all ages but the usual age for the disease to manifest itself is during the third decade It is commoner in women than in men and tends to affect the highly strung rather nervous individual A nervous factor is constantly present and the onset is usually precipitated by psychological difficulties Once established psychological treatment does not cure the condition but nevertheless it is of value to understand the background of the patient Pulmonary complications sometimes produce the presenting symptoms If the cricopharyngeal sphincter fails to prevent regurgitation into the larynx inhalation of œsophageal contents may occur causing lung abscess bronchiectasis or pneumonia Patients have been observed with lipoid pneumonia from taking liquid paraffin The paraffin being of low density floats on the top of the liquid contents of the œsophagus and must seep back into the pharynx when recumbent

An important differential diagnosis of achalasia is carcinoma of the fundus of the stomach Achalasia as a cause of dysphagia presenting in a patient over 50 is very rare and even with the characteristic X ray appearance of achalasia the diagnosis of carcinoma of the fundus must be rigorously excluded by endoscopy and careful follow up

A curious disparity may exist between the size of the œsophagus and the severity of the symptoms and some cases have only slight symptoms with gross enlargement D Silva (1944) reported a symptomless megaœsophagus discovered accidentally from a chest X ray

It has been known for some time that nitrites cause relaxation of the lower end of the œsophagus but amyl nitrite has too much effect on the cardiovascular system to allow its use in treatment as well as diagnosis Field (1944) reported the satisfactory effect of octyl nitrite used in a simple inhaler in four cases of achalasia in children Although there is a suggestion that tolerance to the drug may develop (Robson and Wilkinson 1946) this treatment is a useful therapeutic advance Wooler (1948) does not recommend continued treatment with mercury bougies and has obtained excellent results with the Negus hydrostatic dilator The œsophagoscope is passed under local anæsthesia After cleansing the œsophagus the cardia is sought and dilated with gum elastic bougies up to size 30 The stilette of the dilator is then passed through the cardia and the Negus hydrostatic

mediastinal emergencies The most significant of these are the cyanosis surgical emphysema and grunting respirations In perforated peptic ulcer the pulse is typically slow at first whereas in most cases of perforation of the oesophagus it has been noted in an early stage as thin thready and rapid In his original paper Barrett reviewed the literature of 50 cases of spontaneous perforation but in 1947 reported the first case successfully treated This was a woman of 47 who vomited suddenly while convalescent from a gynaecological operation Signs were found at the right base within four hours a right thoracotomy performed within ten hours and the perforation in the oesophagus repaired

This condition is probably not as rare as the number of subsequently reported cases indicate Early diagnosis is essential for successful treatment It should be suspected in any case in which severe pain in the lower chest or upper abdomen occurs during vomiting An X ray of the chest may show air in the mediastinum confirming the diagnosis

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THE PROBLEM OF PEPTIC ULCER

Peptic ulcer is one of the common illnesses of present day life and the incidence in the population has been the subject of a recent study by Doll Avery Jones and Buckatzsch (1949 1951) From a survey of over 6 000 people mainly in London it was calculated that the incidence of those who have had peptic ulcer in London is 5 8 per cent for men between the ages of 15 and 64 and 1 9 per cent for women in the same age group The incidence of peptic ulcer is found to vary markedly with age increasing in men to a maximum of 9 6 in the age group 45 to 53 and then decreasing A factory employing 1 000 men will thus have nearly 60 workers who have suffered from this malady and over one third of them will have troublesome recurrent symptoms each year If geographical differences are neglected and the age and sex rates are applied to England and Wales as a whole the total number of persons there living who have or have had peptic ulcers is estimated at 1 449 000 while the number of men in each year who suffer from symptoms is estimated at 638 000

Peptic ulcer is not one of the important killing diseases and accounts for only one per cent of all deaths but this represents nearly 5 000 fatalities a year many of which have occurred during the active working life of the individual It is particularly a disease of men (82 per cent) and with the highest incidence between 35—50 it affects men

riboflavin and allied factors the hæmin derivatives cytochrome and cytochrome oxidase are linked in cellular respiratory processes with enzyme systems containing riboflavin and nicotinic acid and riboflavin may be a weak link in the catalytic chain (Stannus, 1940 Pollak 1945) This iron and vitamin deficiency syndrome is still common and much unnecessary invalidism is suffered It is potentially precancerous and many cases of post cricoid carcinoma in women give a history suggesting iron deficiency anæmia (Simpson 1939) A pitfall in diagnosis must be mentioned An angular stomatitis may be caused by ill fitting dentures which allow sagging of the corners of the mouth (Ellenberg and Pollack 1942) Our knowledge of iron metabolism has greatly increased in recent years and an outstanding monograph has recently been published by Vannotti and Delachaux (1949)

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SPONTANEOUS PERFORATION OF THE ŒSOPHAGUS

This rare condition has been the subject of several recent papers which show that the former mortality of 100 per cent is no longer true and that recovery may follow early diagnosis surgical treatment and the use of antibiotics

The clinical picture is well described in a classical paper by Barrett The onset is dramatically sudden The patient, usually after a bout of vomiting is overcome by continuous excruciating pain centred in the region of the xiphoid passing through to the renal area or the base of the chest The complexion is ashen grey with a tinge of cyanosis and the patient is restless anxious and often intensely thirsty The pulse is usually rapid and thin and the brow moist with perspiration The epigastric area may be exquisitely tender with boardlike rigidity of the upper abdominal muscles The clinical picture strongly suggests a perforated peptic ulcer but there are several features which may serve to differentiate between the duodenal and

gastric duodenal ratio In America there is at least a 12 fold preponderance of duodenal over gastric ulcers as compared with a three fold excess in London In only one community—in North Norway (Schanke 1946)—has an excess of gastric over duodenal been recorded It is interesting to find that within the British Isles considerable differences have been reported The figures for Glasgow and Newcastle show a ratio of duodenal to gastric ulcers of at least nine to one One factor responsible for geographical differences may arise from the proportion of town dwellers An analysis of the Registrar General s figures on peptic ulcer shows that mortality rates for men over 45 have been approximately 75 per cent higher in the County of London than in the rural areas of England and Wales

The changing incidence of peptic ulcer in recent years has been particularly interesting and the information with regard to perforated ulcer has been reviewed by Jennings (1940) At the beginning of the nineteenth century when perforations began to be reported more frequently they almost all occurred in young women Between 1850 and 1900 out of every six perforations three occurred in women under 25 and one in an old woman and only two in men Moreover most of the perforations occurred in the region of the cardia In sharp contrast nine out of ten perforations since 1920 have occurred in men while the tenth has usually been in a middle aged woman In men the increase in perforations has been almost entirely found to be in duodenal and juxtapyloric ulcers in young and middle aged men The decreased incidence of acute ulcers in young women during the same period as the increased incidence of duodenal ulcers in men is particularly interesting and demonstrates that improvement in accuracy of diagnosis is not responsible for the changing picture Similar changes have been noted by Avery Jones (1947) in cases of hæmatemesis and from a study of the mortality from peptic ulcer in this country by Tidy (1944) Four aspects of peptic ulcer suggest that environmental factors are of ætiological importance First the great increase in peptic ulcer in recent years secondly the curious geographical differences in the ratio between gastric and duodenal ulcer thirdly the difference in incidence between the social classes and fourthly the variations between occupations Whether such environmental differences arise from changing food habits or from psychosomatic or other factors remains to be solved

Contrary to popular expectation Doll and Avery Jones s Industrial Survey did not reveal any obvious correlation with irregular meals shift work or smoking

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at the peak of their working life The loss of time from work due to peptic ulcer has been recorded by Doll and Buckatszch (1949) who found the total sickness absence attributable to peptic ulcer was 32 4 working days a year per 100 men In the group studied the mean sickness absence of men with proved peptic ulcer was six working days a year more than that of the controls In hospital practice peptic ulcer accounts for approximately ten per cent of the patients in adult general medical and surgical wards and most of these patients are suffering from complications of the disease or undergoing surgical treatment Out patient clinics have at least ten per cent of dyspeptics among their new patients Approximately 60 per cent of these cases have radiological evidence of peptic ulcer (Avery Jones and Pollock 1945) but it is possible that this proportion may have fallen since the war

Much confusion has arisen from consideration of gastric and duodenal ulcer as a single entity peptic ulcer There is increasing evidence that gastric and duodenal ulcers behave differently in many respects and may have different aetiological factors The age incidence differs the expectation of developing a gastric ulcer being greatest between the ages of 35 and 64 while the expectation of developing a duodenal ulcer is maximum between the ages of 20 and 64 The social class incidence is different in the two groups Duodenal ulcers are equally prevalent in all social grades but gastric ulcers show a sharp gradient with social class Doll and Avery Jones (1951) found the observed incidence to be two thirds less than that expected in Social Class I and two thirds more than that expected in Social Class V This confirms the impression from hospital and private consulting practice where it is generally agreed that chronic gastric ulcer was considerably more prevalent in the hospital class than among private patients

There are interesting occupational differences in the incidence of ulcer In the Industrial Survey already referred to a high incidence was found among doctors foremen and business executives i e individuals who are engaged in exacting and worrying work The excess incidence was due almost entirely to a greater number of proved duodenal ulcers The number of gastric ulcers was almost the same as the number expected when age and social class had been taken into consideration A low incidence was found amongst agricultural workers and possibly sedentary workers It was of note that bus conductors and drivers of motor vehicles showed exactly the same incidence as men working in factories

Interesting geographical variations exist too It is said that ulcer is almost unknown in primitive communities Unfortunately there is insufficient evidence to allow a comparison of the absolute incidence in different civilised communities but big variations occur in the

The agricultural worker, possibly more philosophical and phlegmatic, revealed a marked deficiency of duodenal ulcers.

Nevertheless, caution is necessary in accepting a psychological trauma as the sole precipitating influence. In a wartime Glasgow study Illingworth, Scott and Jamieson (1944) found that a peak of perforations occurred before actual bombing and attributed the rise to the general effect of fatigue. Greater irregularity of meals due to transport difficulties or fire watching duties may have been contributing factors. Many sufferers from duodenal ulcer can keep their ulcers in check provided they can avoid long intervals without food. Any acute anxiety may diminish the appetite, interrupt meal habits, and lead to an increase in smoking or alcohol consumption, which may have the cumulative effect of turning a small erosion into a chronic ulcer or of precipitating hæmorrhage or perforation.

It is very remarkable that the acute anxiety of pregnancy in an unmarried woman apparently never leads to peptic ulcer. The rarity of ulcer during pregnancy has been observed by Sandweiss (Sandweiss, Saltzstein and Farbman, 1938), who found only one case in 72 000 pregnancies. There may well be hormonal protection in the stomach in women during the reproductive period of life.

In clinical practice it is difficult to assign more than a small proportion of ulcers in men to a single outstanding emotional episode, but without doubt there is a significant correlation.

The over-energetic, over-conscientious members of the community probably expose themselves more intensely to a number of factors which favour peptic ulcer. They live more intensely, miss more meals and get more tired than their more placid neighbours.

The recognition of the psychological aspects of peptic ulcer has the virtue of therapeutic application. If the tensed-up, over-active individual can relax, he can ease the strain on his digestion. If the doctor can listen to the unburdening of a tragic tale, often untold to other ears, he may relieve a nervous tension. If the patient can learn to appreciate the inter-relation between mind and stomach, he may be able to minimise his dyspepsia at times of stress.

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Psychological Aspects of Peptic Ulcer

Many clinicians think there is a particular personality associated with peptic ulcer These patients are tense possess unusual drive and are over conscientious in their work They tend to worry unduly but do not give way to their emotions

The personality characteristics of ulcer patients the relation of psychological factors to events such as exacerbation hæmorrhage and perforation, and the physiological background of these relationships are dealt with at greater length in chapter XII

Bockus estimates that 50 per cent of ulcer subjects show obsessional or anxiety personality traits Gainsborough and Slater (1946) found 42 per cent of ulcer patients more energetic than average and 84 per cent of men and 69 per cent of women had a mood predominantly anxious They found the chief characteristics of the group as a whole compared with what are met with elsewhere in psychiatry were an energetic disposition tendencies to anxiety irritability and obsessionalism fitting in with the well known 'obsessional' temperamental type Their findings were in agreement with those of other workers (Davies and Wilson 1937 Robinson 1937 Draper 1942) They do not find the ulcer patient neurotic in the narrow sense he is not hypochondriacal or given to complaining nor is he a frank anxiety or compulsion neurotic

The second important psychological aspect of peptic ulcer is the association of acute emotional episodes with the precipitation of a relapse, hæmorrhage or perforation Remarkable case histories have been given by Davies and Wilson (1939) showing a close association with financial difficulty or illness or misfortune in the family and the observations of Wolf and Wolff enable one to visualise a possible mechanism whereby nervous tension and anxiety can precipitate a relapse of peptic ulceration

The results of the occupational survey mentioned previously are consistent with a psychosomatic basis for duodenal ulcer There was a definite correlation between 'anxiety at work' and the frequency of duodenal ulcer Managerial posts carrying responsibility and its resultant worries provided an undue proportion of duodenal ulcers

Price and Lee (1946) have studied factors preventing auto digestion of the stomach and have established that the stomach can digest all living tissue with the exception of gastric epithelium so long as it is protruded into the gastric cavity Some tissues are more resistant than others and Lee and Price have tentatively listed them in order of increasing resistance

(1) Seromuscular coats of intestine and gall bladder
(2) Omentum cartilage
(3) Kidney spleen lung liver and pancreas
(4) Fibrous connective tissue skin and intestinal mucosa
(5) Granulation tissue

The only tissue which was completely immune was gastric epithelium The most significant aspect of their work however was that once the tissue was digested down to the level of the gastric stoma it became covered with fibrous and granulation tissue and further digestion ceased

Analysing the factors concerned in peptic activity Le Veen and Hallinger (1947*a*) confirmed that hydrochloric acid itself is incapable of producing ulcers Hydrochloric acid acts by making the substrate more sensitive to the digestive action of pepsin According to the same authors (1947*b*) auto digestion does not take place because of the presence of inhibitory substances (peptones) which may occur naturally but are certainly produced in the course of normal digestion The result of the presence of these substances is that in the normal resting gastric juice 99 0—99 9 per cent of the pepsin present is in activated

It is possible that the reason gastric digestion did not take place below the level of the gastric stoma in Price s and Lee s experiments is that those inhibitory substances were able to collect in the ulcer while they were easily washed away from the surface of the protruding mass

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Hormones and Peptic Ulceration

Recent years have seen some important developments in our knowledge of hormonal control of gastric motility and secretion and there is a possibility that a hormone may exist which has a protective effect on the stomach against peptic ulcer

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Genetic Factors

Following Hurst it is often assumed that the duodenal ulcer "diathesis" is an inherited condition. Many individual families with striking incidence of peptic ulcer have been reported, of which the most outstanding is Helweg-Larsen. In this pedigree containing 105 members spread over five generations an ulcer was positively diagnosed in 13 and there was evidence of "gastro-duodenitis" in a further 14. The occurrence of ulcer in identical twins is particularly interesting and five pairs with ulcer were reported by Freeman (1947). A number of papers have reported a higher incidence of ulcer in the near relatives of ulcer patients than in controls but these studies have a serious flaw, in that the patient with an ulcer is more likely to be interested in searching out similar cases in his family than the patient who suffers from some entirely unrelated disease. To overcome this objection a survey of the general relation is needed and making use of the Industrial Survey previously mentioned Doll and Buch have established firmly that there is a significant excess of ulcers in the brothers, sisters and fathers of those suffering from peptic ulcer. It was particularly interesting to note that there is a strong tendency for siblings to have ulcers in the same site irrespective of whether the site was duodenal or gastric.

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Physiological Studies

The most significant recent studies are in relation to the method of hydrochloric acid formation, to the factors preventing auto-digestion of the stomach and to protective hormones. The mechanism of acid formation has been the subject of extensive studies by Davies and Longmuir (1946), whose work demonstrates that the secreting cell is like an electric battery with different potential on the two sides. They stress the importance of an adequate supply of carbonic acid within the cell to neutralise the alkali produced at the same time as the hydrochloric acid. In the absence of sufficient carbonic acid disintegration of isolated gastric mucosa occurs at low levels of hydrochloric acid secretion. The initial cellular damage was therefore intra-cellular from excess of alkali rather than extra-cellular from excess of acid.

strongly supports the view that efficient early treatment decreases the chances of subsequent relapses

The first essential is a good history taken in private and with time to discuss the patient s problems A history taken in a hospital ward may easily miss a vital episode which the individual would not mention for fear of being overheard

Rest in bed is most desirable preferably for six weeks Although many ulcers will heal with ambulatory treatment there is little doubt that healing is accelerated and more commonly complete if complete rest is taken preferably away from home where the extra work occasioned by the illness may add to the worry of the patient A period away from home may add perspective to domestic difficulties

Diet There is less emphasis nowadays on elaborate gradations of diet and greater regard for adequate calories and vitamins It is sufficient to have initial hourly or two hourly milk feeds a first diet with small two hourly puree feeds and a basic second diet when pain has subsided still with two hourly feeds This diet should provide at least 2 500—3 000 calories The third diet re directs the emphasis to ordinary meal times but maintains the bland characteristics

The diet should be served in as colourful and attractive a way as possible A bland insipid colourless diet may cause less psychic flow of gastric juice but it makes the patient depressed and irritable The sustained resentment is more harmful than the increased psychic secretion

Extra protein is most valuable At least 90 grams a day is advisable for the basic diet and 120 grams should be given if feasible Dried protein milk e g Casilan and Bemax are two useful ways of increasing the protein content An increase in weight is to be aimed at for a patient who puts on weight usually does well Admittedly ulcers used to heal under a rigid semi starvation regime but then the body proteins were probably broken down to provide the essential factors for tissue repair

Additional fat e g cream butter olive oil is undoubtedly beneficial particularly for duodenal ulcer patients Cod liver oil may be given if tolerated by the patient

Vitamin intake may be augmented by capsules of vitamin A and D Bemax ½ 1 oz daily ascorbic acid 50 milligrams daily

Although pain usually subsides quickly with milk feeds and rest there are some patients whose pain does not cease until they are given a continuous milk drip of six pints in 24 hours

Anti acids Ulcers will often heal without anti acid therapy other than the use of milk (which neutralises an equal volume of 0 3 HCl to *p*H 4) The object of anti acids is not to reduce the *p*H of the stomach to neutrality for this would cause a considerable danger of

Enterogastrone is a hormone derived from the intestinal mucosa which inhibits motor and secretory activity of the stomach Its isolation by Kosaka and Lim in 1930 followed investigation of the well known fact that fats in the intestine have an inhibiting effect on the gastric phase of acid secretion and that this inhibition took place in gastric pouches deprived of any nervous supply

Urogastrone is the name given to a similar gastric secretory depressant which was found in urine by Ivy and his co workers in 1939

Anthelone is an anti ulcer factor named by Sandweiss derived from urine which has been found to have a prophylactic therapeutic and immunising effect against experimental peptic ulcers in dogs

Sandweiss noted the beneficial effect of pregnancy on the symptoms of duodenal ulcer and began an investigation to determine whether there was an endocrine relationship to human ulcer With Saltzstein and Farbman he tested the effect of hormones found during pregnancy on experimental Mann Williamson dogs and in 1938 reported that the extracts of urine from pregnant women had a preventive and curative effect while the œstrogenic hormones had no such action This effect was thought to be due to fibroblastic activity new formation of blood vessels and epithelialisation of the mucosa The extract was shown not to inhibit gastric secretion and had no anterior pituitary like action It was found that urine of normal men has a similar effect though to a much less degree

All these three factors have an anti ulcer effect in the experimental animal It is possible they are one substance and differences in action will be explained by methods of preparation Unfortunately studies in man have not demonstrated any definite benefit

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Management of Peptic Ulcer

There have been no major recent advances in the treatment of gastric or duodenal ulcer a better appreciation of the natural history of the disease has directed the treatment away from the ulcer towards the individual as a whole There are probably few illnesses which need more individual attention than peptic ulcer and yet for which less provision is made in hospital practice Hospital beds are occupied by men and women who have had years of recurrent ulceration and who are admitted with hæmorrhage perforation or for gastric surgery The early case has no chance of hospitalisation unless there are complications There is no statistical proof but clinical experience

instruction leaflet on peptic ulcer may be most useful for patients and reprints of notes on the treatment of indigestion may be obtained in a reprint form from *The Practitioner*

Surgery When recurrent ulceration makes it impossible for the patient to return to work or when the ulcer fails to heal surgery is needed It is likely that the floor of the ulcer may become ischæmic and that healing can no longer take place In these instances the failure is no reflection on the co operation of the patient or on the skill of the physician but is an inevitable result from the scarring and devascularisation in the region of the ulcer For chronic ulceration partial gastrectomy offers excellent prospects of returning the individual to an economic existence Approximately 80 per cent will remain very well after the operation but the remainder may have minor degrees of discomfort from various post gastrectomy syndromes which will be discussed in greater detail

In the majority of these the disability is only slight Taking all patients young and old the total risk of operation carries about a five per cent mortality However in the younger group who are free from associated medical complications the actual mortality is extremely low probably under two per cent This low figure is offset against the higher risk in the elderly and complicated patients No individual should be lightly submitted to partial gastrectomy but all should have thoroughly earned an operation by having exhausted medical therapy The role of vagotomy is not yet finally decided but there is no doubt that vagotomy by itself produces far too many unpleasant side effects and does not provide sufficient protection against further ulceration Whether vagotomy with gastro enterostomy or with a limited gastrectomy will be an improvement over routine gastrectomy remains to be demonstrated but some years must necessarily elapse before the final answer will be obtained

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The Effects of Partial Gastrectomy for Peptic Ulcer

Although the results of partial gastrectomy for peptic ulcer are on the whole excellent nevertheless there are a number of disabilities which may develop and which should be known to physicians These have assumed a greater numerical importance in view of the great number of the gastrectomies performed an increase related to the rising incidence of ulcer in the general population and to the fall in mortality following improved anæsthesia and the introduction of antibiotics Partial gastrectomy is an unphysiological and mutilating

alkalosis, but to reduce the pH to that level at which pepsin activity is inhibited—which Hollander (1939) found to occur probably at pH 3 5 and certainly at pH 5 The subject has been admirably studied by Gill and Keele (1943)

There is no ideal chemical anti acid The requirements for such an anti acid have been given by Beckman (1942) "It is insoluble does not irritate the stomach or intestines does not unduly alter the acid base balance of the body when taken in reasonable amounts will not alkalinise the urine with attendant risks of precipitating crystalline phosphates in the kidney or ureter, will not cause diarrhœa or constipation, and will not seriously alter mineral metabolism "

The soluble anti acids have many disadvantages sodium bicarbonate induces a secondary rise in acidity magnesium oxide and carbonate have the same effect and are too laxative calcium carbonate and bismuth salts are too constipating Calcium and magnesium tribasic phosphates in equal parts appear to have less disadvantages than various mixtures of the preceding soluble anti acids Such proprietary mixtures are often undesirably laxative There is some scope for soluble anti acids Sodium bicarbonate is excellent in relieving pain and may tide over an emergency Magnesium oxide may be a useful aperient in a constipated ulcer subject

Many of the disadvantages of anti acids have been overcome by the development of substances which absorb acid in the stomach and which release the chloride in the intestine The important preparations are *colloidal aluminium hydroxide and magnesium trisilicate* Both absorb pepsin which may be an additional benefit Both can be recommended for routine use during the healing stage of an ulcer It is unnecessary and inadvisable to continue their administration indefinitely when healing has occurred

Sedatives are of great assistance particularly in the initial phase of ulcer treatment Sodium amytal $\frac{3}{4}$—3 grains twice daily or phenobarbitone $\frac{1}{4}$—1 grain two or three times daily are recommended

Anti-spasmodics Atropine or belladona is of particular value given at night to patients with duodenal ulcer and is helpful in controlling night pain A combination of phenobarbitone and extr belladonna sicca $\frac{1}{2}$ grain each in a tablet is recommended one or two tablets being given at 10 p m

Convalescence During convalescence the patient should be given a simple exposition of peptic ulcer A clear understanding of the need for maintaining a calm outlook on life and of the necessity for not exceeding his natural *tempo* by *accepting too much work* or responsibility will be much more valuable than routine medication The patient has got to live with his ulcer forming tendency and it is essential to give him all the information at our disposal A simple

The so called dumping syndrome consists of a sense of fullness and discomfort in the abdomen together with constitutional symptoms such as listlessness fatigue nausea giddiness headaches sweating palpitations and a sense of warmth It is likely that several mechanisms may be involved Sudden distension of the small intestine or the introduction of hypertonic solutions may reproduce the clinical picture and this aspect has been particularly studied by Machella (1949 1950) Capper and Butler (1950) believe that the symptoms are due to the loss of support of the lesser curve allowing excessive splanchnic stimulation by the pull on the œsophago gastric junction They have reproduced the symptoms by placing a mercury weighted balloon in the gastric stump They point out that the symptoms may arise when very little emptying has occurred and that they are prevented by the subject eating while lying down They consider the condition can be prevented by a special operative technique giving greater support to the stomach remnant

They have also cured severe cases of the syndrome by a special operation designed to give greater support to the stomach Gastric distension particularly with aerophagy in patients with a small stoma is another possible cause of the early post prandial syndrome

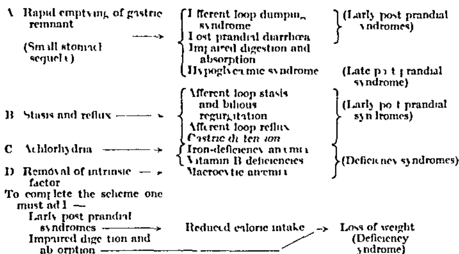
Some degree of iron deficiency anæmia may develop causing lassitude In Wells and Welbourn s series it occurred in 15 per cent of men and 30 per cent of women in the periods between one to ten years after sub total gastrectomy It occurs particularly after the Polya type of operation but only rarely after the Billroth 1 operation Satisfactory absorption of iron depends on the passage of food through the first 12 or 18 inches of the small intestine and if this is by passed surgically iron deficiency anæmia will develop in a proportion of cases particularly if the diet is restricted The response to iron by mouth is usually good but occasionally intravenous iron may be necessary Macrocytic anæmia is extremely rare

The general nutrition in some patients may decline Although there may be some increase in weight after the operation this tends to be lost and patients subsequently fail to gain weight This may be due partly to diminished caloric intake and partly to increased rate of passage through the intestines causing steatorrhœa It is possible that this disturbance of nutrition may increase the susceptibility to tuberculosis Partial gastrectomy particularly the Polya type is to be avoided if there is any history of tuberculosis Some degree of Vitamin B deficiency is not uncommon and Welbourn Hughes and Wells report it in ten per cent of their series It may cause angular stomatitis and glossitis due to ariboflavinosis or paræsthesiæ and muscle cramps due to aneurin deficiency and very occasionally severe peripheral neuritis with œdema or Wernicke s encephalopathy

procedure but one which nevertheless provides excellent relief for sufferers from intractable ulceration At least 80 per cent of patients do very well following operation but the remainder may get various degrees of discomfort and a small proportion probably two to four per cent may develop serious disabilities following partial gastrectomy

Symptoms may arise from loss of the normal "hopper" mechanism of the stomach with the rapid emptying of gastric remnant into the small intestine *Again stasis and reflux of bile or bile and food may* occur from the afferent loop causing discomfort after meals and bilious vomiting

The various post gastrectomy syndromes may be classified as follows (Wells and Welbourn 1951) —



Symptoms may come on soon after eating or two to three hours later The late post prandial syndrome is due to hypoglycæmia following an initial hyperglycæmia soon after the meal the result of rapid emptying of the intestine The hyperglycæmia in itself does not cause symptoms but may stimulate excessive production of *insulin so that the blood sugar falls to hypoglycæmic levels producing* the usual symptoms of hypoglycæmia

The early post prandial syndromes are caused either by the so callep dumping syndrome or to stasis and bilious regurgitation in the afferent loop The patient brings up mouthfuls of bitter tasting fluid after meals and may occasionally have large bilious vomits This is due to stasis in the afferent loop Alternatively food mixed with bile may be vomited due to food entering the afferent loop These symptoms usually improve but occasionally entero anastomosis or jejunoplasty may *be needed to overcome the mechanical difficulties*

300 mg were administered daily by injection Patients with ascites were allowed fluids up to 2 000 ml daily and more in hot weather and salt was restricted Ascites was tapped before gross distension occurred as this impaired the appetite Mercurophylline injections (2 ml) were given once or twice a week and combined with the daily oral administration of 4—6 g of ammonium chloride in enteric coated pills Alcohol was forbidden Much tact sympathy and cajoling was necessary to persuade the patient to eat liberally

The results of treatment were encouraging Out of 124 patients substantial clinical improvement was obtained in 61 cases as judged by the disappearance of ascites jaundice and œdema by gain in weight and strength and by improvement in hepatic function It required several months before significant changes occurred The first sign of improvement was a gain in appetite and feeling of well being Eight per cent of the original group had had ascites before admission to hospital and the average number of previous abdominal paracenteses was 3 5 Diuresis and disappearance of ascites occurred in 50 per cent of those with ascites and the disappearance of œdema parallelled the loss of ascites Vascular spiders were observed in 43 of the 61 patients who improved and in 17 they were noted to have disappeared Cholæmia precipitated by infection or hæmorrhage responded to treatment in 6 out of 19 instances with subsequent survival to months or years When polyneuritis was present there was invariable recovery from paræsthesia motor weakness and atrophy but little change in the result of objective tests such as vibration sense and tendon reflexes The correlation of improvement with laboratory tests was only fair but the value of the serum albumin corresponded most closely to the clinical changes When the serum albumin increased to a value of 4 0 g per 100 ml and remained at that level the patient showed signs of recovery The mean value for serum albumin was 2 8 g per 100 ml before treatment and 4 2 g per 100 ml after treatment

The duration of life after the onset of ascites was significantly better than in the control series At the end of one year 65 per cent of the treated patients were alive and 39 per cent of the controls At the end of two years 50 per cent of the treated patients and 21 per cent of the controls were alive and at the end of five years 30 per cent of the treated patients and seven per cent of the controls were alive It was concluded that cirrhosis hepatis was not of necessity a progressive disease With early diagnosis and treatment the prognosis could be substantially improved

It is probably unnecessary to give quite so much protein but 120 g a day could be easily achieved in Great Britain by using protein milk supplements e g Casilan (Glaxo) Bemax is another useful additional source of protein and vitamin B complex and may be given with milk

The appreciation of these post gastrectomy syndromes is particularly important for the physician. Gastrectomy must be advised for peptic ulcer only after medical treatment has convincingly failed. Although the majority do very well, those who are advised to have gastrectomy must be warned that a small proportion may suffer from minor degrees of discomfort, and also that they should have regular medical supervision at least every six months so that anaemia or vitamin deficiencies may be picked up at an early stage. The nutritional disturbances will be diminished if the patient takes a full diet after operation and in addition takes iron tablets for three weeks twice a year. An additional source of Vitamin B complex such as Bemax or Marmite should be recommended.

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TREATMENT OF CHRONIC HEPATITIS

Considerable improvement may be effected by medical management of patients with cirrhosis even when there is some hepatic decompensation with ascites or haematemesis.

Bed rest is essential initially and the value of a nutritious diet has been well stressed by Patek and his colleagues (1948).

They have analysed the results obtained with cirrhosis of the liver by means of a diet rich in protein and supplemented by concentrates of vitamin B complex. The rationale was based on the frequency of dietary deficiency in patients with cirrhosis and the possibility that malnutrition itself might play an important contributory role. The diet prescribed was rich in protein and ample in carbohydrate and fat containing 140 g. protein, 365 g. carbohydrate and 175 g. fat, a total of 3,500 calories. The diet consisted chiefly of meat, milk, eggs, fruit and green vegetables. Eggs were served with breakfast, meat, fish and poultry were served with dinner and supper, milk was given three times with meals and twice between meals with 25 g. yeast added in the form of a milk nog. If the patient eats these foods considered basic to the programme the remainder of the diet was largely a matter of choice, but the charting of the estimated food intake (1 to 4 plus) provided a stimulus to the patient and served as a useful record. For patients who did not tolerate yeast an oral B complex preparation was given. Aneurin 5 mg. daily and concentrated liver extract 5 ml. twice weekly were given intramuscularly. If the patient showed signs of polyneuritis or mental confusion aneurin 100 mg. and nicotinamide -

4 *Results of operation*

	Males	Females	Total
Operated upon	42	37	79
Died post op	9	7	16
Died during follow up	8	4	12
Alive 6th Jan 1950		26	51

The 12 cases which died during follow up survived from two months up to four years after the operation

5 *General Condition of Followed up Patients*

	Perfectly Well	Moderately Well	Poor
Females ([illegible] cases)	15	7	0
Males (16)	10	4	2

Thirty eight of the 51 cases alive on 6th January 1950 have all been operated on more than a year ago All the 38 cases have been examined during the previous four months The perfectly and moderately well cases comprising in all 36 patients were all active in their pre operative jobs The two poor cases both males were not able to work because of a duodenal ulcer and a subphrenic abscess

6 *Causes of Death during Follow up*

Hæmatemesis with closed shunt	5
open	1
Cholæmia with closed shunt	2
open	1
Perforated ulcer (no autopsy)	1
Hæmochromatosis with open shunt	1
Accidental (pulmonary œdema no autopsy)	1

The 12 cases died in from two months up to four years after the operation Of the five cases who died from hæmatemesis with a closed shunt three had splenorenal shunt made by the vitallium tube technique one a splenorenal shunt by suture and one a portacaval shunt by vitallium tube The one case with the open shunt who died from hæmatemesis had a splenorenal shunt made by suture The two cases with closed shunts who died from cholæmia had a splenorenal and a portacaval shunt made by vitallium tube technique The third case with an open shunt had a portacaval shunt by suture

The experience of the series indicated that a portacaval shunt was preferable to a splenorenal and the suture technique preferable to the vitallium tube technique

Studies in liver function during the follow up showed that 20 per cent of the surgically treated series were improved 20 per cent became worse and 60 per cent did not change

The operation has to be considered particularly in younger subjects with recurrent hæmatemesis especially in the non alcoholic group of patients as in these the function of the remaining liver cells is excellent and the disability arises from the mechanical effect of increased portal pressure

is a cereal. Fresh brewer's yeast may also be given one dessert spoon in milk three times daily. Liver extract intravenously has been strongly recommended by Ralli *et al* (1949) but a suitable extract is not available in this country.

Aureomycin will delay the development of experimental hepatic necrosis in rats (György *et al* 1950) but the evidence is still insufficient to assess its value in man. It would doubtless help when liver failure has been precipitated by an infection.

With the presence of ascites the most helpful measure is to restrict the sodium intake. A cirrhotic patient who is developing ascites can excrete only 1.5 g. by renal and extra renal channels and so every extra gram of sodium chloride represents 100 ml. of retained water in the tissues (Eisenmenger *et al*, 1950).

Surgery for Portal Hypertension

With raised portal pressure causing recurrent hæmatemesis the disease process can really only be modified by surgical anastomosis between the portal and systemic circulation but the operation must be restricted to those with good hepatic function.

The following figures from Blakemore's clinic (Gammeltoft 1950) indicate the present results of surgery in cases with intrahepatic obstruction (e.g. cirrhosis hepatis) treated between 1944–50:—

Results in 79 cases:—

1. *Aetiology of Cirrhosis*

Hepatitis	1
Alcohol	11
Common Duct Obstruction	
Schistosomiasis	–
Various Hepatotoxic Agents	[illegible]
Syphilis	[illegible]
Uncertain	16

2. *Major indications for surgery*

Hæmatemesis or melæna	59
Ascites	10
Cirrhosis and œsophageal varices	9
Chiari's syndrome	1

Ascites was the primary indication in ten cases though 15 cases in addition to bleeding episodes had some ascites at operation; nine cases had general symptoms due to cirrhosis with œsophageal varices shown by X ray but without bleeding episodes.

3. *Type of Portacaval shunt*

Portal vein to vena cava	37 (Died Post op. (	6 16.2 per cent)
Splenic vein to renal vein	39 (	8 20 per cent)
Umbilical vein to vena cava	1 (	1)
Portal vein to renal vein	1 (	1)
Inf. mesentric vein to vena cava	1	

The portal vein to vena cava anastomosis, which is a technically easier operation than the other types mainly due to the size of the veins and the thickness of their walls, has the lowest mortality.

(d) Fat metabolism —
Blood cholesterol
Cholesterol esters
(e) Conjugation tests —
Hippuric acid test
(3) *Empirical tests* —
Serum alkaline phosphatase
Urinary coproporphyrin

Tests Based upon Excretory Function

Van den Bergh Test and Serum Bilirubin In hæmolytic jaundice the direct Van den Bergh reaction is invariably negative while in hepatocellular and obstructive jaundice the direct Van den Bergh reaction is always positive This however is of little value clinically as there are many other features which help to distinguish hæmolytic from other forms of jaundice

The distinction between the direct and indirect reactions is now recognised to be of no practical value and indeed the two types of reactions may not be due to two different forms of bilirubin The real value of the test is in demonstrating jaundice and in allowing a quantitative estimation of the jaundice to be recorded The serum bilirubin is preferable to the icteric index

Urinary bile pigments The presence of urobilinogen and urobilin is determined by Ehrlich s aldehyde test and Schlesinger s zinc fluorescence test respectively Bile pigments are normally reduced to stercobilinogen in the bowel and reabsorbed and re excreted by the liver into the bile The damaged liver may not be able to re excrete the stercobilinogen which is eliminated by the kidneys and gives rise to a positive test for urobilinogen and urobilin With obstructive jaundice the tests will be negative

Dye tests These tests of liver dysfunction are of value only when there is no obstructive jaundice as they are excreted by the bile The most useful one the bromsulphthalein test has been little used in Great Britain as the supply has been difficult

The real function of this test is in assessing hepatic damage in cirrhosis and it is a reasonably reliable indicator of the state of the liver in the absence of jaundice The usual technique is to give 5 mg bromsulphthalein per kg body weight and to take a venous blood sample after 45 minutes when all dye should have disappeared from the circulation

The bilirubin excretion test is little used as it is expensive and technically hazardous

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LIVER FUNCTION TESTS

Liver function tests have been developed in relation to two main demands by the clinician First, to assist him to diagnose hepatic cellular dysfunction in its acute or chronic forms, and secondly to assist him to distinguish between the different varieties of jaundice particularly between extra-hepatic obstructive jaundice and hepato cellular jaundice

Liver Function Tests may be classified as follows —

(Gray, 1950) (1) *Tests based upon the excretory function of the liver*

- (*a*) Serum bilirubin estimation and the Van den Bergh reaction
- (*b*) Urinary bile pigment tests —
  - Bilirubin
  - Urobilinogen
  - Urobilin
- (*c*) Dye tests
  - Bromsulphthalein
  - Bilirubin

(2) *Tests based on the metabolic activity of the liver*

- (*a*) Glycogenic function —
  - Laevulose tolerance
  - Galactose tolerance
- (*b*) Protein metabolism and synthesis —
  - Urinary amino acids
  - Plasma amino acids
  - Serum albumin level
  - Serum globulin level
  - A/G ratio
- (*c*) Flocculation tests —
  - Takata Ara
  - Cephalin cholesterol
  - Colloidal gold
  - Thymol turbidity
  - Zinc sulphate
  - Blood prothrombin and the response to Vitamin K

(d) Fat metabolism —
Blood cholesterol
Cholesterol esters
(e) Conjugation tests —
Hippuric acid test
(3) *Empirical tests* —
Serum alkaline phosphatase
Urinary coproporphyrin

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Tests of Metabolic Function

Glycogen function The galactose and lævulose tests may be used to measure glycogenic function and impairment may support a hepatocellular rather than an obstructive cause for jaundice Both may be metabolised by extrahepatic tissues and this reduces the value of the tests However both the oral lævulose and the intravenous galactose tests may give assistance in some cases With the lævulose tolerance tests (Thompson and Wilkinson, 1940) the normal increase in blood lævulose *should not be greater than 15 mg /100 ml returning* to below 10 mg /100 ml within two hours The galactose tolerance test is advocated by Maclagan (1940) This galactose index should be less than 160 in normal subjects and represents the sum of four blood galactose estimations at ½ 1 1½ and 2 hours after giving 40 G Althausen (1948) prefers the intravenous test and states that the majority of cases of obstructive jaundice gave blood galactose levels of less than 20 mg /per 100 ml 75 minutes after injection of the test dose whereas values over 20 mg /per 100 ml are obtained with cases of hepatocellular jaundice Unfortunately discrepancies tend to occur just in those cases where help is most needed, when jaundice has already persisted for three or four weeks

Protein Metabolism and Synthesis *Urinary and plasma amino acids* are greatly in excess in cases of very gross liver failure Gray (1950) considers it likely that filter paper chromatography may prove a useful guide in lesser degrees of liver dysfunction

Protein Synthesis The diminished synthesis of protein by the liver may be reflected in a change in the serum albumin and in hypopro thrombinæmia With jaundice the presence of inversion of the albumin globulin ratio is greatly in favour of hepatocellular jaundice

The serum albumin is normally between 3 4—6 7 gm /100 ml and is usually *less than 3 4 gm /100 ml in acute necrosis in long standing* hepatitis and in cirrhosis The serum globulin is normally between 1 2—2 9 gm /100 ml and is more than 2 9 gm /100 ml in long standing hepatitis and in cirrhosis

At certain stages of liver disease there is a qualitative as well as a quantitative change in the serum proteins which electrophoresis shows as an increase in the γ globulin fraction This cannot yet be estimated satisfactorily in routine hospital practice but the change is indicated by various flocculation tests such as Takata Ara reaction the cephalin cholesterol flocculation test colloidal gold Scharlach red thymol turbidity and zinc sulphate tests Of these the thymol turbidity zinc sulphate and cephalin cholesterol flocculation tests are the best (Maclagan 1944) Thymol turbidity and flocculation tests are the most frequently used The solutions are easy to prepare and

the test is quickly done More than 4 units suggests hepatocellular damage

The zinc sulphate test (Kunkel 1947) similarly suggests liver damage when reading over 4 units The cephalin cholesterol test (Hanger 1939) is less popular in view of the difficulty of preparation of the reagents

Negative tests do not exclude hepatocellular damage and indeed they may remain negative with massive necrosis of the liver Positive tests in the presence of jaundice are in favour of hepatocellular damage but they may be found in those cases of continued obstructive jaundice with secondary cellular damage

The prothrombin level and the response to Vitamin K may assist in the differential diagnosis of hepatocellular and obstructive jaundice In liver disease the prothrombin time remains prolonged despite adequate parenteral administration of Vitamin K whereas in obstructive jaundice it rapidly returns to normal in most cases Althausen states that 96 per cent of cases of hepatocellular jaundice fail to show a rise of 20 per cent or more in the blood prothrombin level after Vitamin K therapy whereas 90 per cent of the obstructive group gave a satisfactory rise However the response may be negative in some cases of obstructive jaundice of long standing and alternatively some patients with hepatitis may have a normal prothrombin level

Fat Metabolism Observation on the blood cholesterol and the ratio of cholesterol esters may be of some help in differentiating obstructive and hepatocellular jaundice but the estimation of esters is too difficult for routine work The total cholesterol tends to rise with obstructive jaundice and not with hepatocellular jaundice With obstructive jaundice there is a corresponding rise in esterified cholesterol but with hepatic cellular damage the esterified cholesterol may greatly diminish

However it is not a particularly reliable test as the fall in esters may occur with the slight degrees of cellular damage associated with obstructive jaundice

Conjugation of various substances The synthesis of hippuric acid after the administration of sodium benzoate is an unsatisfactory test for Sherlock (1946) has shown that there is very little correlation between it and the degree of cellular damage as determined by liver biopsy Except for occasional use of the intravenous test it has little use in clinical medicine

Serum Alkaline Phosphatase The liver excretes phosphatase into the bile and hence it is retained in cases of obstructive jaundice The normal serum phosphatase is between 4–13 units/100 ml It tends to lie between 13–35 units/100 ml in the majority of cases of hepatitis

and in most cases of obstructive jaundice it is above 35 units/100 ml High readings may sometimes be found in cirrhosis

The common clinical problem is in deciding whether jaundice is due to an intra hepatic process or to extra hepatic obstruction Serum bilirubin estimation, alkaline phosphatase thymol turbidity urinary urobilinogen and urobilin are the most useful investigations to record They represent the maximum of information with the minimum discomfort to the patient, as only one venous specimen of blood is needed, and by comparison with other liver tests they make only modest demands on the Pathological Department

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LIVER BIOPSY

Liver biopsy has proved a valuable aid in the study and diagnosis of liver diseases The best papers on the subject came from Sherlock (1945) Gillman and Gillman (1945) King and Perry (1948) and Terry (1949) and the technique is fully described in these studies The mortality is extremely low and the figures collected by Terry show a mortality rate of 0 28 per cent in nearly 2 500 reported biopsies

Liver biopsy may be of great assistance in the difficult clinical problem of deciding whether jaundice is due to hepatocellular damage or whether it is due to extra hepatic obstruction In the majority of cases the decision can be effected by careful study of the history and biochemical findings but in a few doubtful cases certainty may be achieved by liver biopsy

The indications for biopsy include hepatomegaly where it may reveal inactive cirrhosis hepatitis hæmochromatosis fatty infiltration following malnutrition or alcoholism carcinomatosis Hodgkin s disease or leukæmia The procedure may sometimes be of value also in diagnosing general systemic diseases e g sarcoidosis (Scadding and Sherlock 1948) brucellosis kala azar schistosomiasis and amyloid

disease while the finding of extra medullary hæmopoiesis may point to myelosclerosis

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THE RELATION OF NUTRITION TO LIVER DISEASE

Until a few years ago the only known types of liver injury were those due to certain poisons Next it became clear that similar liver damage could be the result of certain infectious illnesses such as infective hepatitis In 1935 Weichselbaum produced evidence that liver injury might be due not to the presence of a noxious agent but to the absence of an essential nutriment He found that rats on a low protein diet developed hæmorrhages into the liver These hæmorrhages were later recognised as areas of necrosis and in addition fibrotic lesions were produced by deficient diet In 1944 Himsworth and Glynn demonstrated in rats the existence of two distinct sequences of liver injury each due to a different dietary deficiency One led from acute necrosis to a coarse fibrosis of the liver which was termed post necrotic scarring the other led insidiously without any sudden necrosis from fatty infiltration to a fine fibrosis termed diffuse hepatic fibrosis Thus both sequences ended in cirrhosis of the liver

The necrosis sequence was correlated with deficiency of protein and further work showed that the sulphur containing amino acids cystine and methionine prevented the necrosis Methionine is in fact converted into cystine and this cystine deficiency was finally proved to be the responsible factor For a time research workers obtained contradictory results when trying to confirm this work but Paul Gyorgy in 1947 suggested an explanation The experimental diets used varied in their vitamin E content and lack of vitamin E sensitised rats to deficiency of cystine

When it was realised that diffuse hepatic fibrosis was the sequel to heavy prolonged fatty infiltration of the liver Best and his colleagues showed that fatty infiltration might arise in two ways from ingestion of a diet containing excessive amounts of fat or from deficiency of certain dietary factors which normally prevent the accumulation of fat in the liver These were called lipotropic factors and a deficiency of these led to fatty infiltration even when the diet contained no fat The two most important lipotropic factors are choline and methionine

Their common property is the possession of a labile methyl group and it is probable that the lipotropic action of methionine is due to its ability to donate such a grouping and so to augment the supply of choline when this is deficient Methionine can thus serve as a source of choline and cystine and can therefore protect against acute necrosis and fatty infiltration

The fatty infiltration is related to disturbed phospholipid metabolism and occurs within a few weeks on a deficient diet The fibrosis begins close to the central vein and may be found after several months Himsworth and Glynn (1948) believe that the fatty change causes mechanical obstruction of the intralobular sinusoids and this leads to the eventual fibrosis On the other hand Gyorgy and Goldblatt (1949) consider fibroblastic stimulus to arise rather from continued mild necrosis of cells The whole subject has been well reviewed by Watts (1947) Gyorgy (1947) and Himsworth (1948)

Have these experimental lesions their counterpart in disease of the liver in man? Pathologically acute yellow atrophy corresponds with dietetic necrosis and healed yellow atrophy or nodular hyperplasia with post necrotic scarring Turning to the fatty infiltration sequence it can be said at once that fatty infiltration and diffuse hepatic fibrosis indistinguishable from that produced experimentally is well known in man as the cirrhosis of alcoholism

Similarity is not enough to indict nutritional factors for the human pathology but there is more evidence to support the thesis

The broad distribution of liver disease in the world is correlated with malnutrition Acute massive necrosis complicating infective hepatitis in malnourished native races is twenty times as common as among well nourished white troops suffering from the same infection In temperate climates under peace time conditions over half the cases of acute necrosis occur in pregnant or nursing women The general indication is that in this form of liver lesion a positive agent poison or virus is involved as a primary factor and the role of malnutrition is in general confined to that of exaggeration

Considering diffuse hepatic fibrosis in man the evidence is stronger Although traditionally associated with alcoholism *it has long been* known to be common among native races which by reason of poverty or religion never drink alcohol and among such races the condition is also common *in children But wherever the incidence of this fibrosis* is high malnutrition is prevalent

Attention has been focussed recently on a condition first described in *Central Africa and known as kwashiorkor* (Trowell 1949) It is a complex of several deficiency states but it has now been recognised among malnourished people throughout the world Large numbers were *seen in* Budapest during the siege in the last war A common

feature wherever it is found is heavy fatty infiltration and by repeated sampling of the liver the condition has been followed in the same patient from fatty infiltration to diffuse fibrosis It is noteworthy that rats fed on the actual diets eaten by the Bantu races among whom the condition is common have shown the characteristics of acute fibrosis

The explanation of the fatty infiltration is not an excess of dietary fat but a deficiency of lipotropic factors

Can these findings explain alcoholic cirrhosis in temperate climates? Fatty infiltration of the liver has been recognised by French physicians for many years and they thought there were two stages in the development of alcoholic cirrhosis the first with enlargement of the liver from infiltration with fat and the second stage in which the liver was small and fibrotic Fatty infiltration may result from alcoholism because alcoholic drinks contain few if any lipotropic factors over indulgence impairs the appetite particularly for the rich protein foods which supply the factors Alcoholism leads to poverty and still further limits the ability to obtain an adequate diet All these factors cause malnutrition and it is well known that deficiency states are frequent among alcoholics Alcohol itself is probably devoid of toxic effects on liver cells

Deficiency diseases are the expression of intracellular disturbances consequent upon lack of essential nutriments Insufficient nutriments may fail to reach the cells for one of five reasons (Himsworth 1948) There may be insufficiency in the diet Alternatively such toxic factors as trinitro toluene may combine with sulphur containing amino acids and make them unavailable Secondly the intestinal flora may destroy ingested vitamins or synthesise further supplies but there is no evidence that this mechanism affects amino acids Thirdly insufficient absorption may result from a mechanical defect of the bowel Fourthly excessive loss of nutriments may occur as in pregnancy Fifthly there may be a local deficiency within the liver from circulatory disturbances Deficiency of cystine leads to sudden dropsy of the liver cells deficiency of lipotropic factors to prolonged distension with fat and the columns of swollen cells may compress the blood channels which lie between them Hepatic fibrosis may mechanically diminish the blood flow

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VIRUS HEPATITIS

Hepatitis is known to be due to a filterable infectious agent probably a virus There appear to be two distinct forms of the disease infective hepatitis and homologous serum jaundice or syringe jaundice There are distinct differences between them The incubation period of infective hepatitis is between 10-30 days whereas homologous serum jaundice has the very long incubation period of 50-150 days The virus of infective hepatitis is readily transmitted by mouth and is excreted in the stools On the other hand the virus causing homologous serum jaundice is known to be transmitted only by syringe though presumably there must be a natural mode of spread It is not merely a question of different routes of infection producing different incubation periods although the administration of any virus with an immune serum is known to prolong the incubation period The essential difference between the two viruses is shown by failure to demonstrate cross immunity between the two forms of viral hepatitis

There are clinical differences between the illness caused in volunteers by the infective hepatitis virus and by the homologous serum hepatitis virus and these have been summarised by Neefe (1949)

Observation	Infective Hepatitis Virus	Homologous Serum Hepatitis Virus
1 Type of onset	Abrupt	Insidious
2 Constitutional symptoms at onset	Marked	Minimal
3 Fever at onset	Present	Absent
4 Laboratory evidence of hepatic damage in association with clinical report	Delayed 2-7 days	Often present before clinical symptoms

Hitherto experimental work in this field has been greatly hampered by the inability to culture the virus in the laboratory Recently Henle and his colleagues (1950) have transferred serum from patients with infective hepatitis and filtrates of their stools to chick embryo and to rabbit liver tissue cultures After six to ten passes the virus could be adapted to grow in the amniotic cavity of chick embryos It is particularly interesting that cultures now no longer produced frank jaundice but only an illness resembling the mild non icterogenic form of the natural disease The possibility of a live attenuated vaccine is raised A further development is the use of the cultured virus as an antigen for a skin test to distinguish cases of infective hepatitis from homologous serum jaundice

Infective hepatitis is endemic in the population and the distribution is world wide Normally the disease occurs without major outbreaks and children aged 10–14 are particularly affected Many probably have a non icteric form and the illness may even be virtually symptom less Disturbance of the natural equilibrium by the influx of a less well protected population may cause epidemics of the disease and these circumstances together with lower hygiene standard make war conditions favourable for its increase The epidemic involvement of troops in the Middle East during the war illustrates this in recent history Even since the war the incidence of hepatitis among the American troops in Germany has been unusually high and the population of Bavaria is apparently heavily seeded with the virus

Paul and Gardiner (1950) have discussed the disease as it affected the American troops Soon after the end of hostilities in Europe the incidence of infection among them was no less than 17 per 1 000 per annum falling later to about seven The illness in these young men is substantially more severe than the endemic form affecting children

Studies from Denmark (Alsted 1947) and other European countries demonstrate the rising incidence during the war and also draw attention to a particularly severe form occurring in women over 45 and running a malignant course with a mortality of 50 per cent The duration was usually between four and nine months and febrile attacks of right upper abdominal pain were common with development of symptoms of portal obstruction

Acute hepatitis has an astonishingly wide range of clinical activity ranging from afebrile asymptomatic cases to patients with long continued jaundice or acute fulminating hepatitis There is a distinct tendency for relapse to occur during convalescence and this may be provoked by alcohol chilling or exercise

Fortunately well over 90 per cent make a complete recovery and suffer no residual damage to the liver

It has become clear that cirrhosis of the liver is a definite although uncommon sequel of infective hepatitis Thus in a series of 350 patients with infective hepatitis studied carefully by Kunkel Labby and Hoagland (1947) two definitely developed chronic hepatitis with alteration in the A/G ratio It is likely that the majority of cases of cirrhosis in non alcoholics and well nourished individuals may be due to previous hepatitis infection often non icterogenic Infection may indeed begin in childhood In this connection a remarkable story is told by Copps Bennet and Stokes (1950) of an epidemic of hepatitis in an orphanage for infants and children under two years During the course of seven years 71 nurses had developed jaundice On searching for the reservoir of the virus they found that about one third of the infants had several signs of severe liver disease although none had had

jaundice When efforts were made to avoid infection from soiled linen the epidemic among the nurses cleared

Sometimes a syndrome of anxiety, fatigue fat intolerance and right upper abdominal discomfort follows an attack of acute hepatitis This condition has been called the post hepatitis syndrome (Sherlock and Walshe, 1946) The only positive finding is a palpable tender liver edge biochemical tests and liver biopsy are normal

Treatment remains non specific Bed rest is the first essential and the patient should stay in bed until symptom free and until urobilin has disappeared from the urine and the serum bilirubin has fallen to less than 1 mg /100 ml

In view of the role of proteins and their sulphur containing amino acids in the development of experimental liver injury, it was obvious that these should be tried in the treatment of acute hepatitis although it does not follow that they would be beneficial No striking results have been achieved Darmady (1945) found no benefit from treating infective hepatitis with high protein diets Higgins *et al* (1945) and Wilson, Pollock and Harris (1945) have failed to demonstrate any therapeutic effect of methionine in infective hepatitis Choline has proved without effect in infective hepatitis (Richardson and Suffern 1945) and in homologous serum jaundice (Turner *et al* 1944) Peters *et al* (1945) found a slight beneficial effect of cystine in post arsenical jaundice and Wilson *et al* (1946) found some shortening of the period of recovery and fewer relapses in infective hepatitis treated with the oral administration of 5 grams of cystine daily Witts (1947) is doubtful whether the old fashioned treatment of catarrhal jaundice can be improved strict bed rest together with a low fat diet because the patient is unable to assimilate fats and a low protein diet because the metabolism of protein demands work by the liver cells A light diet with plenty of milk from which the top layer of fat has been removed is suitable There is no need to give routine glucose and insulin Once the appetite has returned a very liberal intake should be ensured Convalescence should continue for twice as long as the period of bed rest

Infective hepatitis is an infectious disease which is mainly spread by fæcal contamination of utensils food or water Sudden severe epidemics may be caused by pollution of the water supply Neefe and Stokes (1945) describe an epidemic at a children s camp when 350 cases of infective hepatitis occurred among 572 campers The virus is resistant to ordinary methods of water sterilisation (Neefe *et al* 1945) but boiling water for five minutes *is a definite safeguard* Good bodily hygiene and safe disposal of fæces is essential to reduce the incidence of the disease

Homologous serum *jaundice can be prevented* by vigorous care to

avoid contamination by blood products of syringe and needles used for parenteral injection and boiling or autoclaving is necessary A rapid technique for mass inoculations has been described by Fleming and Ogilvie (1951)

There is a specific risk in the administration of blood or plasma and Neefe (1949) gives the following estimate of incidence

	Incidence of hepatitis
Whole blood	0 6–0 8 per cent
Small plasma pool 5–10 units	1 5
Large plasma pools 1 000–5 000 units	4 5–12

Such a risk is far from negligible and there are clearly circumstances where it may be a deciding factor against transfusion

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ULCERATIVE COLITIS

The cause remains unknown the treatment non specific new cures emerge every year and remain successful for a brief time but all in turn emphasise the great tendency of the disease to remit spontaneously The last treatment and the last physician still tend to get the credit Clinical impression suggests that patients are

improving more satisfactorily than ten years ago, and this may be due to greater interest in the positive aspect of the diet (adequate protein vitamins and calories) and less concern about a ‘ low residue ’ diet There is no doubt that some of the manifestations of the disease in the past have been due to a secondary nutritional deficiency state Rectal complications are now rarely seen since local treatment of the bowel with washouts has become less popular There has been continued interest in the psychological aspects of the disease previously studied by Murray (1930) Sullivan (1936) and Wittkower (1938) However for the chronic cases surgical treatment with ileostomy and colectomy is becoming increasingly popular

The personality pattern of colitis has been the subject of study by Paulley (1950) a general physician without psychiatric training who is convinced that the majority of patients have a definite personality pattern which makes them more liable to over react to threats to their personal security He emphasises their extreme scrupulousness sensitiveness dependence and lack of aggression Appreciation of this aspect is valuable in the management of these patients after the acute episode has subsided

There seems no doubt that emotional crises can pull the trigger which fires a relapse Whether the gun is loaded entirely by psychological factors remains to be solved but it is likely that there are other trigger factors at present unrecognised The prognosis remains poor although complete remission may occur even in severe cases Rice Oxley and Truelove (1950) have studied 129 cases over 11 years at Oxford and their figures give a good impression of the prognosis

Taking the new cases the fatality was worked out in relation to the length of follow up

Length of follow up (years)	No of patients	No dead	Fatality rate %
1	69	15	22
2	61	16	26
3	49	14	28 5
4	45	13	29
5	39	12	31

Of the 72 new cases three were not traced in the follow up

This shows an initial high mortality rate of 22 per cent in the first year with a further ten per cent dying before five years elapsed A further idea of prognosis was obtained by classifying patients according to the type of course which the disease ran

Group	Course of disease	No of patients and % of total
I	Acute fulminating a single attack going on to death in less than 1 year	15 (0 8)
II	Chronic intermittent more than one attack with at least several weeks complete freedom between attacks	27 (37 [illegible])
III	Chronic continuous continuous symptoms for more than 1 year	18 ([illegible]0)
IV	Single attack followed by complete freedom	10 (13 9)
V	Unclassified follow up failed	2 (8)
	TOTAL	[illegible]

In correlating the mode of onset with the subsequent prognosis they found that excluding the acute fulminating group among 31 patients followed up for one to five years there were eight patients who had had only one attack The chance however of these developing a subsequent attack is brought out by the 23 patients followed up for 6–11 years when only two had not relapsed

Analysis of the series in relation to age and sex showed that these had little influence on the subsequent course of the disease In addition to its lethal qualities ulcerative colitis is important as a source of chronic illhealth as shown in the following table —

Degree of Activity (New Cases only)

Course of disease (group)	DEGREE OF ACTIVITY			TOTAL
	A (normal)	B (restricted)	C (invalid)	
II	10 (40)	14 (56)	1 (4)	2[illegible]
III	6 (3 /)	8 (50 /)	2 (1 5)	16
TOTAL	16 (39 /)	[illegible] (53)	3 (7)	41

It is clear that although 40 per cent are living a normal or near normal life about 50 per cent are moderately incapacitated while only a small number are totally incapacitated

In the same series the incidence of complications is as follows –

Cutaneous lesions	9 3 per cent
Arthritis	5 4
Stricture	5.4
Fæcal fistulæ	3 9
Carcinoma	3 1

There was thus an appreciable incidence of skin and joint lesions often occurring together The type of skin rashes were as follows —

	No of cases
Erythema nodosum (3 with arthritis)	4
Erythematous rashes	2
Pustular rashes (1 with arthritis)	3
Purpura (1 with arthritis)	1
Ulceration of legs (with arthritis)	1
Urticarial rash	1

In five cases these lesions were minor and transient but in the remaining seven they appeared as major episodes The simultaneous appearance of erythema nodosum and arthritis has been reported previously but it is not widely known

The presence of metabolic derangements has been increasingly recognised and these are discussed by Posey and Bargen (1950) *Urinary excretion of 17 ketosteroids is diminished* and the adrenal reserve function is impaired as measured by the adrenalin test on the eosinophil count Evidence of calcium deficiency may be found with osteoporosis and potassium deficiency may be revealed by the typical electrocardiographic changes

The liver may show pathological changes particularly fatty change which may lead on to cirrhosis Jones Baggenstoss and Bargen (1950) found moderate or severe fatty changes in 47 out of 91 cases with three examples of cirrhosis of the liver These changes are probably the result of malnutrition and possibly of toxaemia from the colitis

The risk of carcinomatous changes in the intestine is probably increa ed Cleckler and Brown (1950) found 12 cases among 316 patients (3 8 per cent) The association with colitis is strengthened by certain features Multiple carcinomata are particularly common and the average age of onset (39) is considerably younger than the general population The average duration of colitis previously has been given as nine years There is no definite correlation between the polyposis of chronic colitis and neoplastic degeneration

The studies on the personality underline the need for patient *individual handling of each sufferer* Probably more help will be given from a careful study of environmental factors than by deep psycho analysis Conscious effort must be given towards maintaining the patient s morale The patient must always have some special innocuous treatment to which he may pin his faith Unnecessary repetition of investigations must be avoided A relapse can be induced by a further sigmoidoscopic examination and if this is under taken the patient must be assured that improvement has occurred Occupational therapy can be a real boon to these long stay cases

The bland diet should provide at least 2 500 calories and 120 grams of protein Extra protein may be given as dried protein milk Bemax

soya flour and gelatine Vitamin supplements should be given Blood transfusions of 540 cubic centimetres at a time are often essential to maintain the hæmoglobin above 80 per cent Recent new treatments such as desiccated ileum and thiouracil have not withstood the test of time The introduction of antibiotics has not greatly influenced the prognosis

As with peptic ulcer surgery is becoming the accepted treatment for those patients with persistent severe symptoms or frequent relapses and remarkable results are possible from ileostomy followed by colectomy Brown Cleckler and Jones (1950) report a mortality of only four per cent in a series of 64 cases excluding the acute toxic patients in whom the risk is much higher They strongly advocate that routine colectomy should follow the ileostomy within two to six months The difficulties of an ileostomy must not be minimised but are reduced by the use of a special bag such as the Kœnig Rutzen bag described by Hardy and his colleagues (1949) An easily disposable adhesive bag has also been devised by Clayton Jones (1950)

Primary excision of the colon with ileostomy is advocated in selected cases by Bacon and Trimpi (1950) and it is likely that this will be undertaken more frequently in the future once colectomy is recognised to be a necessary sequel to ileostomy

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MEGACOLON

The work of Swenson and Bill (1948) in America and Bodian Stephens and Ward (1949) in Great Britain have made important contributions to our knowledge of the condition described by Hirschsprung in which there is gross enlargement of the colon Swenson and

Bill found that in 20 cases of typical Hirschsprung s disease there was a spastic segment causing partial obstruction and the actual megacolon terminated at some point proximal to the anus It appeared that the megacolon was secondary to the obstruction and that apart from its enlargement the bowel was elsewhere capable of a normal function The spastic segment was incapable of peristaltic action and the reason for this was clearly demonstrated pathologically On microscopic examination, the intramural nerve plexuses were found to be lacking in ganglion cells and the cause was thus a congenital aplasia of the ganglion cell

Another abnormality is the presence of non medullated nerve bundles, sometimes of considerable size present at the usual site of the intramural plexuses The rest of the bowel shows hypertrophic muscle coats with normally arranged ganglia In most of the cases the aganglionic zone usually terminates well below the junction of the sigmoid and descending colon, but in about ten per cent of cases there is a long aganglionic segment which may extend to the splenic flexure to the hepatic flexure or even involve the entire colon and a portion of the terminal ileum Bodian Carter and Ward (1951) have described a case with complete absence of intramural ganglion cells distal to the duodenojejunal junction but in this particular case unlike the other cases there were no abnormal nerve fibres in the bowel wall - The incidence of this aganglionic defect is very small and probably occurs in about every 20 000 to 30 000 live birth

Bodian Carter and Ward (1951) have studied the hereditary aspects and find evidence of a familial tendency The chances of a male sibling of a known case being affected are about one in five

The precise nature of the embryological defect has yet to be discovered as the origin of the intestinal neurones is still under discussion On embryological grounds the disturbance probably occurs between the thirtieth and the thirty fifth day of fœtal life

There are two groups of megacolon manifesting themselves in early life In addition to these cases with a demonstrable anatomical lesion in the bowel there is also a group of idiopathic cases thought to be due simply to chronic constipation In Hirschsprung s disease boys are affected many times more commonly than girls and the condition causes symptoms very early in life there may be retention of the first meconium stools Bowel actions become irregular with long intervals between them and gaseous abdominal distension appears early In about two thirds of the cases there are obstructive crises with vomiting sudden abdominal enlargement and constipation in the first six months The child becomes dehydrated and loses weight the abdomen becomes tense and considerably distended If the child survives these early difficult days the disease enters a chronic stage

the abdomen becomes permanently enlarged and inflated the ribs flared out and diaphragm elevated In the abdomen writhing peristaltic waves are easily visible but on palpation the fæcal masses tend to be masked by the associated gaseous distension On rectal examination the anus appears normal and the rectum is empty and not dilated Acute attacks of obstruction intervene from time to time and hitherto cases of Hirschsprung s disease have rarely reached adolescence

The clinical picture of idiopathic megacolon due to chronic constipation differs in several respects from that of true Hirschsprung s disease The onset of constipation is usually later usually after two years The motions become dry hard and infrequent and defæcation is painful This leads to passive loading of the rectum and sigmoid with firm fæcal masses which are easily palpable Some abdominal enlargement develops but this is not so gross as in Hirschsprung s disease and peristaltic waves are seldom visible Retention overflow may occur with fæcal incontinence simulating diarrhœa with small pieces of fæces being constantly passed through the anal canal The general health of the child is usually well maintained and the major abdominal crises characteristic of Hirschsprung s disease seldom occur These cases may be treated adequately by wash outs given at first daily until the rectum is clear and continued at intervals for some weeks In the true cases of Hirschsprung s disease very encouraging results have followed surgical treatment aimed at resecting the abnormal segment of bowel and restoring continuity

Bodian *et al* (1949 1950 1951) have reported the results in 37 cases There were three deaths in the series and two operations were done too recently for inclusion in the follow up The remaining 32 children are all in excellent general condition all but one pass regular and spontaneous motions and only half are receiving aperients

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CHAPTER IX

METABOLIC DISORDERS

by

GEORGE A SMART

Diabetes Mellitus   Disturbances of water and electrolytes   Potassium imbalance   Isotopes   Folic Acid and Vitamin B_{12} Osteoporosis and Osteomalacia

DIABETES MELLITUS

Ætiology The isolation and subsequent therapeutic use of insulin has not only stimulated a vast amount of research in diabetes mellitus but also has provided workers with an essential tool for their investigations Much of the knowledge has been gained by means of animal experiments and it is only now that its clinical importance is *being realised*

Houssay and his co workers found that removal of the pituitary produced hypersensitivity to insulin and that this hypersensitivity was removed by injections of extracts from the anterior pituitary Later they showed that depancreatised dogs lived longer and were more nearly normal if they also had the pituitary removed Extracts of anterior pituitary when injected into these animals caused a return of diabetes of great severity Houssay then found that injections of anterior pituitary extract into intact animals gave rise to a resistance to the action of insulin and to glycosuria which recovered spontaneously *in spite of continued injections of similar quantities of anterior* pituitary extract (Houssay and Magenta 1929 Houssay and Potick 1929 *Houssay and Biasotti 1930 Houssay, 1936) Young (1937)* found however, that if the injections of anterior pituitary extract were increased in amount it was possible to maintain the glycosuria and if after a sufficient time these injections were then stopped

permanent diabetes was produced That this diabetes could be prevented by the simultaneous administration of large doses of insulin was demonstrated by Haist Campbell and Best (1940) who also showed that the animals are protected if they are either on a low calorie or on a high carbohydrate diet They found moreover that the injection of anterior pituitary extract diminished the insulin content of the pancreas and that the insulin content was increased by a diet high in carbohydrate Cats rendered permanently diabetic by injections of anterior pituitary were cured by insulin therapy if only short intervals were allowed to elapse before its institution (Lukens and Dohan 1940) On the basis of these experiments therefore it would seem that the syndrome of diabetes mellitus can arise either because excess secretion from the anterior pituitary may give rise to insulin resistance or because of poor secretion of insulin from a damaged pancreas This latter condition might occur as a result of a temporary overactivity on the part of the anterior pituitary and the fact that diabetes tends to occur at puberty and at the menopause may be of significance in this connection Further rapid progress is to be expected from animal experiments since the discovery that alloxan specifically destroys the β cells of the islands of Langerhans thereby producing the diabetic syndrome

By a series of well designed experiments on human subjects Himsworth (1939) has been able to throw much light upon the diabetes mellitus syndrome He was able to show that some subjects lost much more glucose in the urine than was ingested in the form of carbohydrate and that even though extra glucose loss was induced by causing a diuresis the high blood sugar level was maintained It thus appeared that the high blood sugar level in diabetes mellitus, far from being a passive accumulation as a result of its lack of removal from the blood was actively maintained by the body Himsworth suggests that since the central nervous system can for practical purposes only obtain its energy from glucose the level of this sugar in the blood is actively maintained at a high level thus compensating to some extent for the difficulty created by the lack of insulin It also follows that if excessive urinary loss of glucose is maintained for any length of time other dietary constituents must be actively converted into carbohydrate There is no reliable evidence that such a transformation occurs from fat but there is no doubt that amino acids can be and are converted and that ketone bodies arise as a by product

In a further series of investigations Himsworth showed that the changes in blood sugar level which follow the injection of a given dose of glucose depended upon the preceding diet of the subject A previous diet high in carbohydrate was associated with a flat glucose tolerance curve whereas a low carbohydrate intake was

CHAPTER IV

METABOLIC DISORDERS

by

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finally broken down to carbon dioxide and water or whether it is converted into fat

It seems possible in the light of this work that any one of several biochemical abnormalities might result in the syndrome of diabetes mellitus

The discovery by Hench of the effect of Cortisone on rheumatoid arthritis has focused much attention on the role of the hormones of the adrenal cortex in carbohydrate metabolism The mild diabetes associated with Cushing s syndrome has long been known as has been the tendency to hypoglycæmia in patients with Addison s disease and it is evident that the gluco corticoids from the adrenal cortex cause the deposition of glycogen in the liver and possibly also cause the development of some insulin resistance The fact that there is an increase in uric acid output after the giving of cortisone or ACTH and that there is a structural similarity between uric acid and alloxan which was shown by Shaw Dunn and McLetchie to destroy the β Cells of the islands of Langerhans has resulted in further interesting speculations concerning the aetiology of diabetes

Conn *et al* (1949) have shown that after ACTH there is not only an increased output of uric acid but that there is also a fall in blood glutathione Furthermore in temporary diabetes produced in a young man by giving him ACTH the blood sugar could be reduced to normal levels by the giving of glutathione It is suggested that there may be some disturbance of purine metabolism whereby a toxic substance like alloxan is produced which in its turn produces diabetes However Stoel and Currence (1950) were unable to find abnormalities in the blood levels of reduced glutathione or of uric acid in 14 fasting ambulatory diabetic subjects although it should be noted that the mechanism suggested by Conn *et al* need only be temporary giving rise to permanent pancreatic damage

Recent work on the role of vitamins of the B complex in the diabetic state are of interest It has long been shown that the insulin requirement of diabetic dogs becomes progressively greater if they are fed on a diet of low vitamin content Gaebler and Ciszewski (1945) found that the inclusion of yeast in the diet of depancreatized dogs was very effective in reducing the glycosuria and loss of weight and nitrogen which occurred In experiments on one animal they obtained evidence that aneurin riboflavin and nicotinic acid prevented the nitrogen loss and that inositol was probably a factor in ameliorating the glycosuria In the clinical field Biskind and Schreier (1945) maintain that they found evidence of B complex deficiency in all of 94 diabetic patients These improved in general health and required less insulin under intensive vitamin therapy and the authors suggest that a long standing vitamin B complex deficiency might impair liver function,

followed by a raised glucose tolerance curve, at times simulating that obtained in a subject with mild diabetes It was shown that this change in glucose tolerance was due to a change in the effect of insulin A diet rich in carbohydrate increased a subject s sensitivity to insulin whereas he became more resistant when the carbohydrate intake was low When the insulin sensitivity of diabetic subjects was investigated there were found to be two main groups one insulin sensitive and the other relatively insensitive In general the insulin sensitive group is composed of young, thin diabetics who easily become hypoglycaemic and who rapidly develop ketonuria The insulin resistant group is composed of middle aged or elderly hypertensive diabetics who are only rendered sugar free with difficulty who can tolerate large doses of insulin and who do not easily develop ketonuria It seems therefore that the disease which has in the past been called diabetes mellitus is composed of at least two distinct conditions and interesting confirmation of this comes from the field of anthropometry where it has been possible to separate patients with diabetes into two distinct physical types which agree closely with those described by Himsworth It has of course long been recognised empirically that fat and thin types of diabetics existed

Ketone bodies in part produced when protein is converted to carbohydrate are also formed in the metabolism of fats, but there is little evidence that the mechanism of β oxidation does in fact occur in the body—it is not strictly true that fats are burned in the fire of carbohydrates Rather it would seem that fatty acids are broken up into a series of ketone bodies in one process Furthermore there is considerable evidence that ketone bodies can form a very useful source of energy for muscle metabolism and it is probable that under resting conditions the body can metabolise ketone bodies to the equivalent of 2 5 grams of fat per kilogram body weight per day—i e about 175 grams of fat per day for a normal adult male

An interesting suggestion has been put forward by Lawrence (1946) that one of the main functions of insulin is to facilitate the transformation of glucose to storage fat Recent work on diabetic animals using *glucose labelled with heavy hydrogen* substantiates this hypothesis The diabetic syndrome would occur under these circumstances when the subcutaneous tissues were unable to store fat either as possibly in Lawrence s case because of some preventing hormone or because of previous overloading such as might obtain in the obese middle aged diabetic who responds so well to a reduction in weight

It has been shown by Price Cori and Colowick (1945) that both insulin and a hormone from the anterior pituitary are concerned in the preliminary phosphorylation of glucose which is necessary before the further metabolism *of this substance can take place* whether it is

chosen contained a high proportion of fat and only small amounts of carbohydrate together with large quantities of yeast or crystalline vitamins On the average there was a decrease in calorie intake of about 25 per cent the intake of vitamins increased threefold When the rats were placed on a stock diet however the symptoms of diabetes rapidly recurred

The only gauge of the success of a particular diabetic regime is in the resultant health and progress of the patient and since the advocates of the various types of diet all claim good results it would appear that within reason and with insulin therapy one particular type of diet has little merit over another The position is of course complicated by the fact that published series have not been separated into insulin sensitive and insensitive types and it is probable that the requirements of these two groups are quite different

The introduction of insulin has revolutionised the prognosis of diabetes mellitus and it is now true to say that the main problem is no longer the therapy of the diabetic state but the prevention of the complications associated with it Pure crystalline insulin may be inconvenient to use since its short action (four to six hours) involves multiple injections (two or more per day) and since it may not be possible to adjust the dosage to control adequately the ketosis of severe insulin sensitive diabetics without frequently precipitating them into hypoglycaemic coma A great advance was therefore made by Hagedorn and Jensen who by combining insulin with a protamine obtained a compound which was only slowly absorbed from the site of injection and which therefore had a prolonged action The stability of this insulin compound was greatly increased and its action further prolonged (40 to 48 hours) by the addition of zinc More recently zinc globin insulin and zinc histone insulin have been introduced with actions somewhat intermediate between insulin and protamine zinc insulin Which of these compounds is used much depends upon the severity of the diabetes and upon social and economic circumstances of patients For example since the action of zinc protamine insulin is prolonged it is necessary to disperse the carbohydrate intake over many meals throughout the day An intake of 250 grams carbohydrate might be distributed thus —

Breakfast	*10 o clock*	*Lunch*	*Tea*	*Supper*	*Nightcap*
50 grams	2 grams	50 grams	3 grams	50 grams	40 grams

This might be very inconvenient for people in certain types of employment who might prefer to have two large meals a day each preceded by an injection of standard insulin and two smaller meals without insulin Many physicians find that optimum control is obtained by combining protamine zinc insulin with ordinary insulin and giving one injection per day Since there is an excess of protamine

with resultant failure of the organism to respond to endogenous insulin, and so produce diabetes mellitus

Treatment One of the main controversies in the correct treatment of diabetes mellitus concerns the question of diet Some authors advocate high fat and low carbohydrate diets others *high* carbohydrate diets and yet others insist that no dietetic restrictions are necessary Joslin (1940) points out that the incidence of diabetes in obese persons is very much higher than in those of normal or less than normal weight On the assumption that obesity *produces* diabetes he therefore advocates that diabetics should be given a diet with a calorie value such that a weight slightly below normal is maintained On general grounds this is probably sound since insurance statistics demonstrate that the mortality rate from practically all causes is greater in the obese Richardson and Bowie (1945) also attempt to keep their patients below average weight and the diets which they give only contain 1 600–1 900 calories High carbohydrate diets are championed by Rabinovitch (1935) who believes that they result in a lower incidence of tuberculosis and of arteriosclerosis and in the light of Himsworth s investigations such diets would seem to be advantageous Stolte (1931) and Lichtenstein (1945) allow their patients to eat what they like and then adjust the insulin dosage so that ketonuria is abolished and only slight glycosuria occurs Lichtenstein s patients chose diets which on the average contained about *6 to 7 grams of carbohydrate, 2 to 3 grams of protein* and *2 5 to 3 5* grams of fat per kilogram body weight per day The daily calorie value per kilogram body weight was about 90 for children under five years 70 for those between five and ten years and 50 for the over ten years old Tolstoi (1949) whose diabetic patients are clinically rather than chemically controlled also advocates the use of a free choice of diet in diabetics requiring insulin and finds that among his patients there is no greater incidence of vascular lesions or other complications than has been found in chemically controlled diabetics His criteria for treatment are —

(1) The patient must receive a long acting insulin
(2) The patient must not be ketotic
(3) The patient must be free from all symptoms

There is some experimental evidence in favour of this *free choice* of diet Richter and Schmidt (1941) and Richter Schmidt and Malone (1945) presented rats in individual cages with a variety of *foodstuffs in separate containers so that the* actual amounts eaten per day by each rat could be determined Standards were obtained for the healthy rats and the pancreas was then removed It was found *that the* symptoms of polydipsia polyphagia and loss of weight did not occur when the free choice of diet was allowed and that the diet

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in protamine zinc insulin however, it is important that careful trials should be carried out with each make and batch so that the effect of the added insulin can be adequately gauged Two new preparations NP 50 and NP 40 have been marketed in the United States which contain exact proportions of protamine and insulin and so overcome this difficulty It is claimed that more exact control is possible with these preparations but even so it is not possible to continue the necessarily strict dietary regime in the majority of diabetics to maintain 'chemical normality' Globin insulin can be used for those patients who develop allergic manifestations with protamine zinc insulin since it rarely produces such hypersensitivity It has also been found that 'brittle' diabetics who tend to oscillate from symptoms of thirst to hypoglycæmia within 24 hours can often be controlled more evenly by means of two injections per day of globin insulin the morning and evening dose being varied as required This method results in greater flexibility than can be obtained when zinc protamine insulin is used and it has the advantage over the use of soluble insulin that there are no periods without substantial insulin action

On what criteria must one decide that a patient requires insulin? A working rule used by Duncan (1942) is that no diabetic who is over weight is initially given insulin and that all underweight diabetics receive it from the outset He points out that whereas a small reduction in the weight of obese diabetics from a restricted diet and/or from an increase in exercise is very often sufficient to control the diabetes up to 100 units of insulin daily may be necessary to produce the same effect Also, he contends that the insulin resistance shown by most of these obese diabetics is lost with a reduction in weight Similar views are expressed by Newburgh and Conn (1939) who claim that complete cure of the diabetic state may be obtained It should be noted however that these results have not been confirmed by other workers Occasionally an elevated glucose tolerance curve may become normal after weight reduction but as pointed out by John (1950) the diabetic tendency is still present and frank diabetes may recur with a subsequent increase in weight or intercurrent infection In general it may be said that diabetics who are underweight who have ketonuria or who have complications should receive insulin whereas those who are obese and who have no ketonuria nor serious complications should be treated by dietetic means It should be emphasised that this dietetic regime should aim at a reduction in weight and should therefore be of low calorie content (not more than about 1,500 per day) this is if anything more important than ensuring a reduced carbohydrate intake

Whatever dietary regime is adopted a moderate control of carbo hydrate intake so that it remains about the same from day to day

with the free choice of other nutrients is favoured by the author—the dosage of insulin if this is necessary being so adjusted that the urine is free from ketone bodies and of moderately low sugar content

To maintain a urine free from ketone bodies is considered to be of the utmost importance Diabetic coma is the most frequently preventable serious complication of diabetes and in most hospitals it has a high mortality rate Although the immediate cause of diabetic coma is not known it rarely if ever occurs without preceding ketosis If therefore patients with diabetes were to test the urine once each day for ketone bodies and were to seek medical advice whenever ketones were present in abnormal quantities they would have a fairly good insurance against falling into coma The ferric perchloride test is not satisfactory for this purpose because of its false positives and because of its relative insensitivity Rothera s test on the other hand is too difficult to be carried out by the less intelligent patients who are precisely those requiring most guidance With this in mind the author and Mr G Darling have devised a powder test for ketone bodies which is really a modified Rothera s test The composition of the powder is as follows —

Ammonium sulphate	87 0 per cent
Anhydrous tribasic sodium phosphate	12 5
Sodium nitroprusside	0 5

These components are intimately mixed together If kept dry in a well stoppered container the powder will last for a considerable time The test is performed by moistening a small pile of the powder with one or two drops of urine The colour which is the same as that of the orthodox Rothera s test reaches its maximum intensity in about three minutes The author has only seen two of the patients who use this test admitted to hospital in coma one of these had previously requested admission and had been refused and the other had been in another hospital for an operation and the control of his diabetes was in the hands of the hospital staff ! On the other hand several have reported with considerable ketosis which was rapidly and easily abolished by suitable increase in the insulin dosage A powder similar to the above is now obtainable ready made in the U S A

Complications There has been little published work concerning the effect of modern treatment on the incidence of the *complications* of diabetes mellitus The series of papers by Richardson and Bowie (1945) Edeiken (1945) Leopold (1945) and Naide (1945) in which 100 diabetic patients of ten or more years standing have been studied are therefore welcome These patients were kept on a diet supplying only 1 600 to 1 900 calories and consisting of approximately 70 grams protein 90 grams fat and 160 grams carbohydrate Few of them were considered to be badly controlled and diabetic coma only occurred on three occasions all patients recovering

The incidence of hypertension increased with age and it was about twice as high among women There were markedly less cardiac changes however, both clinically and electrocardiographically than in a comparable series of non diabetic hypertensives It was also suggested from the figures that the high proportion of carbohydrate in the diet resulted in a diminished incidence of arteriosclerotic changes

It appears also that lens opacities were not so frequent as among poorly controlled diabetics and there is some indication that a slight diminution in the incidence of diabetic retinopathy follows careful control

Joslin (1950) and John (1950) have recently reviewed the incidence of complications in their large series of diabetic patients with substantially similar findings The outstanding feature is the high incidence of death from cardio renal disease and the paper by Goodman Wasserman Marcus and Frankel (1950) which presents the results of their study of atherosclerosis in diabetics is therefore of great interest Their cases ranged from 18 to 91 years of age the great majority being over 50 A very high proportion had evidence of atherosclerosis but in contrast to the findings of Priscilla White (1945) who worked on a group of juvenile diabetics they could find no correlation between general evidence of this lesion and the presence of retinopathy Also they could not confirm White s findings of calcification occurring in the leg vessels and extending to the aorta indeed in the gangrenous limbs they examined the whole artery was found to have become a fibrous cord without any evidence of thrombosis having occurred as a terminal event in a calcified vessel On the basis of these differences they suggest that the lesions of retinopathy and intercapillary glomerulosclerosis are probably quite different entities from the vascular disease occurring in non diabetic individuals

It has often been asserted that very careful chemical control of diabetes during treatment renders the onset of vascular complications less likely but there is little evidence for this Indeed the experience of Tolstoi (1949) and of Dolger (1947) suggests that there is no difference in the incidence of vascular disease in well controlled and in poorly controlled diabetic subjects

A careful description of diabetic retinopathy has been given by Ballantyne and Lowenstein (1943) They point out that there are three principal features which characterise the condition

(1) *Hæmorrhages* These may be the only evidence of the retinopathy Typically they are round or spindle shaped and occur in the centre of the fundus particularly in the region of the veins The earliest appearances however may easily be overlooked since they consist of minute punctate

hæmorrhages (or perhaps aneurysms) particularly round the macula

(2) *Exudate* Minute punctate areas which are situated chiefly in the centre of the fundus and tend to coalesce to produce larger areas with a lardaceous appearance

(3) *Changes in the Veins* These consist of localised dilatations tortuosities diverticulæ and reduplications The appearances are quite characteristic of diabetes and histological studies show that fatty deposits are laid down in the vessel walls In severe cases detachment of the retina or thrombosis of the central vein may occur These gross abnormalities of the veins may occur in mild diabetics and in patients who are well controlled The prognosis is bad so far as the sight is concerned but the general prognosis for the patients is little altered

The problem of diabetic neuropathy has been carefully reviewed by Rundles (1945) He points out that the condition is not a presenting symptom of diabetes but arises in long standing and often neglected diabetics frequently being associated with loss of weight hepatomegaly and retinitis It is he asserts essentially a painful condition and particularly affects the lower limbs although it may be asymmetrical Half the cases show loss of vibration sense and of muscle joint sensitivity Superficial sensation is also affected but not so severely There also may be Argyll Robertson pupils and these together with the ataxia which results from the loss of muscle and joint sensation produce the syndrome of diabetic pseudo tabes It is stressed that the autonomic nerves suffer equally with the others and that as a result visceral disturbances may occur such as nausea constipation postural hypotension impotence and atonic bladder A role to these autonomic changes is also ascribed in the production of gangrene and trophic ulcers in the leg One cannot agree with the implications of Rundles however that diabetic peripheral neuritis is essentially painful It *may* be but very frequently the only evidence is lack of tendon reflexes found on routine examination and complaints of pins and needles or burning or numbness in the fingers and feet are very much more common than true pain

The possible ætiology of diabetic peripheral neuritis is considered and the conclusion is reached that the condition is toxic in origin It is pointed out that the theory that nerve degeneration is secondary to a thickening of the nutrient arteries cannot be substantiated since some of the cases occurred in young subjects with no evidence of arterial disease The possible nutritional origin of the condition after careful review is also dismissed since it is contended that other deficiency signs are absent On the other hand Rudy and Epstein

(1945) in a review of 100 cases of diabetic neuropathy maintain that there was a frequent association of signs and symptoms of a B complex deficiency They suggest that the deficiency is produced rather by the abnormal metabolism than by a poor dietary intake Since several of the vitamins of the B complex are concerned in carbohydrate metabolism it certainly seems to be possible that a conditioned deficiency might be produced by the profound disturbance which occurs in diabetes mellitus and recently the author has himself seen a diabetic with peripheral neuritis evidence of cord and cerebral lesions and with superficial glossitis angular stomatitis and pellagrous skin lesions Further careful studies into the incidence of signs of vitamin deficiency in diabetics *and in a comparable group of normal subjects* is necessary before any definite conclusion can be reached

A rare but interesting complication is mentioned by Lawrence (1949) *In these cases although a very marked resistance to insulin* develops (a case of the author s required 750 units of insulin per day) if insufficient insulin is given thirst polyuria and ketosis ensue The onset of the resistance is usually within a year of first starting insulin and it usually disappears gradually after some years the dosage of insulin having to be gradually diminished towards the end of this period

Diabetic Coma Much controversy exists concerning the correct treatment of diabetic coma All authorities of course agree that insulin must be given in large quantities (50 to 100 units per hour at the beginning of treatment) in order to allow normal carbohydrate metabolism to occur with a consequent abolition of the ketosis All agree that the extreme dehydration of diabetic coma should be treated with large volumes of intravenous fluid and all agree concerning the importance of a thorough search for a precipitating cause of the coma but there is strong argument over the merits or harm of giving glucose The viewpoint championed by Joslin (1940) is to regard the giving of glucose to be not only unnecessary but also definitely harmful The reasons to quote Joslin are as follows —

(1) Glucose is already flooding the blood and body tissues generally in the patient with diabetic coma and can be utilised just as satisfactorily as injected glucose if adequate amounts of insulin are supplied (2) Under certain conditions added glucose may precipitate renal block (3) Serial determinations of blood sugar afford an excellent guide to treatment during the first several hours in hospital Obviously such values are robbed of their significance if a constant infusion of glucose is being carried out

This reasoning is upheld by Root (1945) who attributes a considerable fall in the mortality rate of his cases of diabetic coma to the

giving of larger doses of insulin early in treatment to the giving of large volumes of intravenous saline and to the withholding of glucose

On the other hand as pointed out by Duncan (1942) the liver and tissues of subjects in diabetic coma are severely depleted of glycogen and there cannot be more than 20 to 30 grams of glucose in the circulation Since the comatose condition of the patient can to a great extent be correlated with the degree of ketosis and not with the related hyperglycæmia since the utilisation of glucose is necessary to prevent the formation of ketone bodies and since as pointed out by Peters (1945) the presence of hyperglycæmia facilitates the combustion of glucose it would seem that glucose should be very advantageous The precipitation of glucose in the renal tubules is probably secondary to and not the cause of a reduced urinary secretion It is possible that the anuria which sometimes occurs is the result of pituitary disturbances and the circulation of an anti diuretic hormone as postulated by Brun Knudsen and Raaschou (1946)

Attention has recently been directed to the occurrence of the potassium deficiency syndrome in cases of diabetic coma which have been treated in the orthodox way Usually before treatment patients in diabetic coma have a normal or rather high serum potassium level During the course of treatment however this may fall to very low levels and may be accompanied by the onset of muscular weakness and sometimes of respiratory paralysis Changes in the electrocardiogram are also not infrequently seen and these are similar to those occurring in association with low serum potassium levels An investigation of these changes has been carried out by Martin and Wertman (1947) who found that sagging of the S T segment was frequently present before treatment was commenced and that this usually disappeared within 24 hours After one to four days of intensive therapy many of the cases showed a prolonged Q T interval but except where this was extreme there was no definite association with low serum potassium levels There was however a high degree of correlation between depression of the T waves and low serum potassium levels the T waves increasing in amplitude with the return of the potassium to normal levels It would seem that many factors in diabetic coma influence the electrocardiographic appearances and that one of these is the depressed extracellular potassium level which tends to occur during therapy

It was shown as long ago as 1933 in the classical work of Atchley Loeb Richards Benedict and Driscoll (1933) that patients with diabetes who were allowed to become acidotic by witholding their daily insulin lost potassium in excess of nitrogen and that this potassium was retained during subsequent therapy A similar type of experiment has more recently been carried out by Butler Talbot Burnett

Stanbury and MacLachlan (1947) who confirmed their findings and suggested that attempts to rehydrate patients in diabetic coma with normal saline resulted in the giving of far too much sodium and that part of the cause of the lowered serum potassium during treatment was the enhanced glucose metabolism which occurred indeed the possible deleterious effects of glucose in diabetic coma might result from the production of a more rapid and greater lowering of extra cellular potassium *Phosphate is also retained in large quantities* during therapy and as a result of their studies the following solution has been evolved for intravenous use in cases of diabetic coma —

Sodium lactate	2 2 g
Potassium chloride	1 0 g
Potassium phosphate di basic	0 5 g
Sodium chloride	0 6 g
Water distilled to	500 ml

50 ml of this solution contains approximately 30 m Eq of Na 19 m Eq of K 23 m Eq of Cl and 8 5 m Eq of phosphate For use it should be added to one litre of five per cent or ten per cent glucose solution and the precautions given in the section on Potassium should be taken

There has been some recent evidence that variations in the activity of the adrenal cortex are of importance in altering the severity of diabetes mellitus McArthur Sprague and Mason (1950) found that the excretion of urinary corticosteroids was two to eight times higher during diabetic acidosis than it was during recovery and subsequently By a close metabolic study of diabetic dogs McArthur *et al* (1950) have confirmed that increased adrenal cortical activity occurred during the onset of diabetic ketosis resulting solely from the withdrawal of insulin This increased cortical activity began quite late in the acidosis and was roughly associated in time with the onset of vomiting it was followed by a great increase in the output of potassium It is a possible cause of the known resistance to insulin action found in cases of diabetic coma

Increased activity of the adrenal cortex may also play a part in the precipitation of ketosis in diabetics Such increased activity occurs in association with infection and also almost certainly in abnormal emotional situations Hinkle Conger and Wolf (1950) report the case of a juvenile diabetic where emotional disturbances resulted in the onset of ketosis

Owing to the severe loss of nitrogen which occurs in uncontrolled diabetes it is possible that the serum protein might be considerably depleted This would produce no symptoms during the period of dehydration but when large volumes of saline were given œdema might be precipitated The author has recently treated two such cases in whom with the onset of œdema the serum proteins were

4 1 and 4 7 grams per 100 millilitres respectively It would be wise therefore if some of the fluid administered intravenously were in the form of solutions of plasma proteins Furthermore it should be remembered that these patients sometimes live exclusively on carbo hydrate for several days Thus a supplement rich in vitamins of the B group should be advantageous particularly as it has frequently been observed that the onset of diabetic neuritis may occur shortly after the commencement of therapy with carbohydrate and insulin

Stomach wash outs are advocated by several authorities since these not only reduce the risk of aspiration pneumonia but assist in reducing the acidosis

Pregnancy and Diabetes Diabetic women who are adequately treated have a normal fertility rate but they are especially liable to some of the complications of pregnancy In the first place there is an increased incidence of abortions miscarriages and still births The increase is diminished as the diabetes is controlled but still births are approximately six times more frequent even among well controlled diabetic women than among normals This is partly due to the tendency to produce large babies (which may occur many years before the mother actually develops diabetes) and partly to the frequent occurrence of toxæmia of pregnancy Work of importance in this condition has been published by Smith and Smith (1940) who found that the onset of toxæmia could be predicted by a rise in chorionic gonadotropin and that in some cases this rise could be prevented by œstrin and progestin In this country Loraine (1949) also found that 6 of 14 pregnant diabetic women excreted abnormally high amounts of chorionic gonadotropin in the urine Stilbœstrol therapy produced a fall in these high levels which however was only temporary White (1940) has been very enthusiastic over the findings of Smith and Smith and has given clinical details of 51 pregnant diabetic women treated in her clinic Twenty of these whose serum gonadotropin was repeatedly normal had uneventful pregnancies 11 in whom the serum levels became abnormally high all developed complications—eight toxæmia and three premature deliveries and 17 who showed increased serum levels but who received continuous therapy with œstrin and progestin developed no serious complications In a more recent publication White (1945) points out that there are four groups of abnormality which occur much more frequently in pregnant diabetic women than in normal pregnant women —

(1) Maternal vascular disease and maternal hypo ovarianism
(2) Obstetric complications namely early spontaneous abortion (25 per cent of cases) pre eclamptic toxæmia (36 per cent of cases) breech presentation (33 per cent of cases) uterine inertia and failure of lactation

(3) Chemical abnormalities which include the development of a low renal threshold for glucose water retention and hormone imbalance

(4) *Fœtal abnormalities which might be (a) physical* such as a high birth weight and a high incidence of congenital defects (*b*) chemical, manifested by a low blood sugar, respiratory difficulties on the first day and almost universal icterus and (*c*) pathological including enlargement of the liver spleen and heart and hyperplasia of the pancreatic islets

White gives the following table of results for 181 cases —

	No of Cases	Premature Delivery	Toxæmia	Fœtal Survival
Hormone balance normal	52	0	2 %	96%
Hormone balance abnormal	38	40%	50 %	50 %
Hormone imbalance treated	91	15	Much less*	90 %

* At first treatment only initiated after symptoms of toxæmia were manifest but latterly when treatment was begun on chemical grounds the incidence of toxæmia was reduced to 5 per cent

These results are certainly encouraging but it should be emphasised *that much of the work is not controlled sufficiently for an adequate* appraisal to be made

The influence of pregnancy on diabetes is often unpredictable In general if the condition is uncontrolled it is found that it becomes more severe until about the sixth month when amelioration begins possibly due to commencing hypertrophy of the fœtal pancreas If the diabetes is controlled by insulin it is usually found that the requirements continue to increase until term when there is a great tendency for the onset of hypoglycæmia If the patient has been stabilised on protamine zinc insulin it is a wise precaution to change to ordinary insulin at this stage and to revert to protamine zinc insulin during the puerperium

Congenital abnormalities are about twice as frequent in the children of diabetic mothers as in the general population and the neonatal mortality also is high *Death is usually due to asphyxia variously* attributed to cerebral injuries from excessive moulding of the large foetal head or to hypoglycæmia possibly consequent upon hypertrophy of the islet cells of the fœtal pancreas It is held by Nothmann (1941) that Cæsarian section should be performed as a prophylactic measure to save the life of the child He gives figures which show that babies from diabetic mothers have very low blood sugar levels and often become comatose from which condition they recover immediately if glucose is given intravenously It is known that shortly after birth

the babies of normal women may have very low blood sugar levels but clinical evidence and the frequent post mortem finding of a hypertrophied pancreas lends some weight to the possibility that the death of an infant of a diabetic mother may be due to hypoglycaemia Some authors therefore recommend that glucose should always be given to the newly born infants of diabetic mothers but many think that this is unnecessary Probably the most satisfactory course is to treat all babies of diabetic mothers as if they were premature

Intercapillary Glomerulosclerosis Mention should be made of the syndrome of intercapillary glomerulosclerosis consisting clinically of diabetes mellitus albuminuria œdema and hypertension This association was first described by Kimmelstiel and Wilson (1936) and later by Newburger and Peters (1939) who found the pathological changes to be quite distinctive they consist of the deposition of hyaline material in the centre of all the renal glomerular tufts There are usually retinal changes similar in character to those of malignant hypertension and there seems to be little association with any particular type of diabetes mellitus As mentioned above this capillary disease is one of the major hazards encountered by juvenile diabetics

Diabetic Gangrene Prophylaxis against this serious and not infrequent complication should be started early All diabetic patients should be instructed concerning the importance of wearing well fitting shoes They should be instructed to keep the feet clean and to attend a competent chiropodist if necessary Any epidermophytosis which is present should always be treated and all diabetics



FIG 1 The foot of a patient after the removal of the great toe and the first metacarpal for diabetic gangrene

over 40 should be forbidden to walk about at home without shoes or slippers on since infection and trauma are often the precipitating factors in gangrene (Figures 1 and 2)



Fig 2 The toes of a patient who had refused a high amputation for diabetic gangrene 18 months before this photograph was taken

Chemotherapy has assisted in revolutionising the treatment of this condition No longer are high amputations necessary, in fact the more conservative and the less traumatic the surgery the better The part should be kept dry, infection should be controlled by chemotherapeutic measures and plenty of time (two to three months if necessary) should be allowed before surgery is considered Figure 1 illustrates the results of such therapy and figure 2 shows the foot of a patient 18 months after she had refused to have the mid thigh amputation advised by a surgeon

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total body content of those electrolytes is about 2 174 m Eq (50 grams) of sodium and 4 487 m Eq (175 grams) of potassium Or again in congestive heart failure the level of serum sodium may be low nevertheless because of the vastly increased volume of extracellular fluid the total body content of sodium is abnormally high With these difficulties in mind let us examine anew the mechanisms whereby the body regulates water electrolytes

Figure 3 shows in a diagrammatic form the distribution of water in the various body compartments About 50 per cent of the body

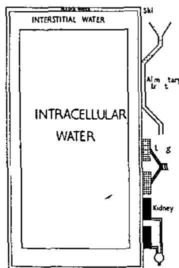


Fig 3 Showing the relative volumes of water in the three body compartments The areas of the compartments are proportion l to the volumes of water contained in them

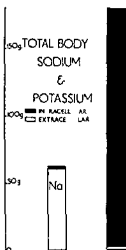


Fig 4 Showing how Sodium and Potassium are distributed between the extracellular and intracellular compartments

weight consists of intracellular water about 15 per cent of interstitial water and about five per cent of plasma water Figure 4 shows diagrammatically the distribution of sodium and potassium the two main basic ions of the body Obviously it is important to consider the factors concerned in the transfer of water and electrolytes to and from the body as a whole and from one to another of the three main compartments

Under normal circumstances water and electrolytes only reach the body fluids by way of the gastro intestinal tract The body loses water via the bowel skin lungs and kidneys and electrolytes via the bowels skin (in active sweating) and kidneys Both water and

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DISTURBANCES OF WATER AND ELECTROLYTES

Very great advances have recently been made in the understanding of the bodily regulation of water and electrolytes Much of the basic work has been carried out by Gamble (1947) and this has an important bearing on the therapy of those conditions associated with water and electrolytic abnormalities

It is necessary at the outset to emphasise that information relating only to the gravimetric weight of a substance has little chemical significance It is much more convenient to work in 'equivalent weights , one equivalent weight being defined as the atomic or molecular or ionic weight of a substance in grams divided by the valency

In considering the electrolytes of the body a milliequivalent is the unit usually used and one milliequivalent of an ion is its ionic weight in milligrams divided by its valency Thus one milliequivalent of sodium is 23 mgms , one milliequivalent of potassium 39mgms and so on

Furthermore since most of the osmotic pressure of the extracellular compartment is regulated by sodium (the total acid ions are adjusted to be equivalent to the total basic ions by changes in the bicarbonate level) which is monovalent and since potassium also monovalent is the main intracellular basic ion the use of milliequivalents has the added advantage of giving a clear indication of the relative osmotic effects of these substances (In fact for monovalent ions 1 milli equivalent = 1 milliosmol)

It is important also to realise that the levels of electrolytes in the urine do not necessarily give a true reflection of the levels in the serum since the kidney is by no means always regulated automatically according to serum levels Furthermore serum levels of electrolytes do not necessarily reflect the total body content of those electrolytes since this depends upon the concentration of the electrolytes in the extra cellular and intracellular compartments and upon the total volume of water in those compartments For example in normal man the serum level of sodium is about 140 m Eq per litre (330 mg per 100 ml) and that of potassium is 5 m Eq /1 (20 mg per 100 ml) whereas the

Dehydration

As has been shown by McCance and his co workers and by Marriott (1950) dehydration can result from a deficiency of water or from a deficiency of salt or from a combined deficiency of these two substances. The syndrome of pure water deficiency is quite distinct from that of pure salt deficiency and the distinction is very important for the rational treatment of a dehydrated patient.

Salt Dehydration Deficiency of sodium with no lack of water results in a fall in the osmotic pressure of the extracellular fluid. Sodium is conserved by the kidney probably in part by the increased secretion of adrenal cortical hormones and a diminution in the production of anti diuretic hormone results in the production of a dilute urine. In this way the osmotic pressure of the extracellular fluid is restored at the expense of its total volume which becomes diminished.

Symptomatically subjects dehydrated as a result of sodium deficiency are not thirsty but characteristically suffer from langour and apathy. In addition there is quite definite muscular weakness and easy fatigue ability. Headache particularly on standing is liable to be present and there is also a tendency to giddiness and fainting. The eyes become sunken and the skin wrinkled with loss of elasticity there is loss of weight which might amount to about 1 kgm for every 3 4 g of sodium deficit and muscular cramps may be present. Anorexia nausea and vomiting frequently occur and as pointed out by Marriott this only aggravates the condition leading to a vicious circle. Mental changes such as confusion disorientation and stupor may also occur. Finally the patient passes into a state of oligæmic shock the result of the diminution in circulatory fluid volume and subsequent hæmo concentration. The skin is cold and clammy but the blood pressure at first is maintained the diastolic even being higher than normal later however the blood pressure becomes low the venous pressure is lowered and peripheral cyanosis appears. At this stage stupor and even sudden death may occur. The urinary volume may remain fairly good until near the end.

Marriott has also observed that there appears to be a very definite ileus of the alimentary tract fluid remaining in the distended stomach for long periods. He postulates that a definite spasm of the pylorus occurs in association with sodium depletion.

Biochemical investigation reveals that there is very marked hæmo concentration as shown by the hæmatocrit and hæmoglobin levels a decrease in plasma volume as measured by Evans Blue Dye and a decreased plasma sodium and chloride. Owing however to the regulating mechanism of the kidney this decrease may only become of significant degree late and Marriott contends that it is much more satisfactory—and certainly much easier—to use Fantus (1936) test

electrolytes are lost from the mouth when vomiting occurs, or gastro intestinal suction is carried out Unless active sweating occurs the loss of water from the lungs and skin the insensible loss, remains fairly constant at 1,000–1 500 ml per day for an average adult The total body content of water and electrolytes is normally regulated mainly via thirst and appetite on the one hand and via the kidney on the other Little is known concerning the regulation of appetite and thirst, but much has recently been learnt of renal mechanisms

It is well established that the renal control is exerted mainly by a process of differential reabsorption of glomerular filtrate by the renal tubules How much of this process is automatic is not known, but it is certain that a considerable influence is exerted by hormones Anti diuretic hormone elaborated in the posterior pituitary has a profound influence on the reabsorption of water When this hormone is absent less water is reabsorbed by the tubules and so a diuresis occurs when present in greater quantities the tubules reabsorb a large amount of water and only small amounts of highly concerntrated urine are passed Verney (1946) has postulated the presence of osmoreceptors which are sensitive to changes in extracellular osmotic pressure When this falls e g after the ingestion of large amounts of H_2O the osmoreceptors detect the change and cause the posterior pituitary to liberate less antidiuretic hormone into the blood stream as a result less water is reabsorbed and a diuresis occurs Since relative to plasma concentration more water is lost than sodium the osmotic pressure of the extracellular fluid tends to return to normal By contrast if the extracellular fluid becomes more concentrated than normal greater amounts of ADH are liberated with the result that only small quantities of concentrated urine are elaborated

The reabsorption of Na and K by the renal tubule is regulated by some of the hormones elaborated by the suprarenal cortex There is no precise knowledge concerning this regulatory mechanism since the exact effect of a given steroid upon the kidney may vary according to the amounts of other steroid hormones present It seems, however that so far as the mineralo corticoids are concerned increased secretion leads to retention of Na and loss of K and vice versa Fuller Albright s team (Fourman *et al* 1950) have shown that this is also true for Compound F Hormones from the suprarenal cortex also probably have some regulatory effect on the transfer of K and Na between the intracellular and extracellular body compartments With these facts in mind it is possible to consider some of the main problems in the treatment of dehydration and generalised œdema and of certain derangements of body electrolytes but it should be pointed out that there is some mutual interaction between adrenal corticoids and anti diuretic hormone the nature of which is not yet understood

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for urinary chloride Ten drops of urine are placed in a test tube by means of a pen filler which is then rinsed and used to add one drop of 20 per cent potassium dichromate solution (used as an indicator) After further rinsing the same filler is used to add a 2 9 per cent silver nitrate solution drop by drop with vigorous shaking after the addition of each drop until the colour changes from yellow to red brown The number of drops of silver solution required indicates roughly the number of grams of chloride (expressed as NaCl) there are per litre of urine In general if the urine contains five or more g per litre and the patient is not suffering from Addison s disease nor has been receiving saline infusions he is unlikely to be suffering from salt depletion A word of warning however is essential Under certain conditions, and not infrequently post operatively no chloride is eliminated in the urine even though there is no bodily deficiency Furthermore it is assumed in the application of this test that urinary chloride levels reflect those of sodium this assumption is quite unwarranted and is often erroneous The test is a useful approximation and better therapeutic control will be obtained with than without its use

The syndrome of salt deficiency outlined above occurs in any condition where there is adequate fluid intake coupled with abnormal loss of sodium and chloride from the body If the intake of sodium and chloride is also low the condition will occur more rapidly A hot environment is probably the commonest predisposing condition considering the world as a whole but in this country diarrhoea and vomiting is the most frequent single cause for the condition It should be remembered that normal gastric juice contains about 20 m Eq Na per litre as well as about 120 m Eq Cl per litre

Water dehydration Water dehydration is produced whenever the *loss of water from the body is greater than the intake According* to Marriott this occurs in two main circumstances (*a*) In emergency conditions such as shipwreck where water is not available and (*b*) where there *is inability or disinclination to swallow* such as *occurs in* any seriously ill patient in patients with dysphagia from any cause and in comatose patients

In such pure water deficiency there is a tendency for the osmotic pressure of the extracellular fluid to increase As a result of this an increase in antidiuretic hormone production occurs and the kidneys *begin to secrete only* a small volume of highly concentrated urine In addition water moves from the intracellular to the extracellular phase In other words *water deprivation results in cellular dehydration by contrast with salt deprivation which results in extracellular dehydration*

In such patients there is thirst which is usually progressive dryness of the mouth with decreased salivation and a small volume of highly concentrated urine The minimum volume of urine secreted under

these conditions is about 300–500 ml for an adult and the specific gravity may rise to as high a figure as 1 040 After three or four days a certain amount of muscular weakness becomes apparent the face assumes a pinched grey appearance and there may be some exaggeration of the usual emotional reactions with at a late stage confusion and hallucinations The cause of death is unknown but that the increase in the osmotic pressure of the body fluids may be a cause is suggested by McCance

Water taken by mouth is rapidly absorbed and may result in improvement within a few minutes This is in marked contrast with the poor absorption found in salt deficiency

Generalised Œdema

In considering the production of generalised œdema it must be noted that the mechanisms postulated by Starling concern the balance of fluid between the plasma and the tissue spaces across the capillary walls Any disturbances such as increased capillary pressure or decreased plasma protein which result in a tendency for fluid to shift from the plasma to the interstitial spaces can only result in generalised œdema if there is a retention of fluid within the body as a whole It is necessary for the tissue space fluid volume to increase by at least ten per cent before clinical œdema is apparent and if this is generalised it represents in a 70 kgm man a volume of about 1 litre which the plasma must lose Since there are normally only about 3 5 litres of plasma water this would represent a loss of about 30 per cent necessary to produce a just perceptible œdema Everyone can recall cases of œdema with ascites where the ascitic volume alone was much greater than the average 3 5 litres of plasma water Furthermore although the plasma and intracellular levels of sodium may be slightly lower than normal when there is generalised œdema the increased extracellular fluid volume is so great that the total body content of sodium is very greatly increased

It can be seen therefore that in patients with œdema resulting from for example congestive heart failure the water and electrolytic alteration is more or less the reverse of that seen in sodium dehydration As might be expected diminution of œdema occurs if the excessive amount of sodium in the body can be eliminated This can be achieved by a diet very low in sodium (not more than 0 5 g NaCl per day) and by the prevention of tubular reabsorption of sodium by organic mercurials and possibly as proposed by Schwartz (1949) by sulphonamides The elimination of sodium results possibly by the hormonal mechanisms outlined above in an equivalent elimination of water and consequent reduction in œdema Restriction in the intake of water is of little use in the treatment of the generalised œdema of cardiac failure in

fact there is considerable evidence that, provided the intake of sodium is low an intake of water of the order of 8 litres per day is more helpful in reducing the œdema since it results in an additional outpouring of sodium Water intoxication may however, result from these measures if the initial serum sodium level is too low

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POTASSIUM IMBALANCE

The study of body potassium has in the past been difficult partly because of the rather lengthy and elaborate chemical estimation required and to a greater extent because serum potassium levels do not necessarily reflect the state of total body potassium Figure 5 shows the proportionate relationship between sodium and potassium in serum and between total body sodium and potassium Furthermore of the 175 grams of body potassium only 2 5–3 0 grams are extra cellular and this cannot vary greatly and still remain compatible with life Much greater variations in intracellular potassium can and do occur and they are not necessarily accompanied by changes in plasma potassium concentration which can only be determined by careful and complicated balance studies or by the use of radioactive potassium By these two techniques it has been shown that there is little correlation between intracellular potassium and

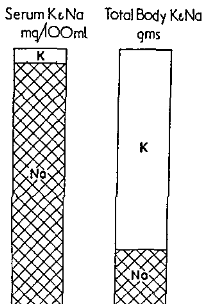


FIG 5 The relative serum concentrations of sodium and potassium and the relative total quantities of these elements in the body

the serum concentration of potassium except that when the serum potassium is low it is almost invariably associated with low levels of intracellular potassium (Burrows and Sisson 1950 Darrow 1950 Elkinton Winkler and Danowski 1948)

In studying the factors involved in distribution of potassium it is necessary to consider —(*a*) the total balance of the body as a whole with regard to potassium and (*b*) the factors involved in the distribution of potassium between extracellular and intracellular fluid (*a*) Under normal conditions the daily intake and output of potassium is about 4 g Most of the loss occurs in the urine and when the intake is deficient the kidney can only conserve potassium to a limited extent the urine never having a lower potassium concentration than the serum—it is usually much higher and the loss of large quantities of potassium in the urine is dependent upon a good urinary flow Loss of potassium can also occur when intestinal secretions are lost as in diarrhœa and intestinal fistulæ the potassium content of these secretions is about that of the plasma Gastric secretion contains a concentration of potassium two to four times as high as that of the plasma and considerable quantities can thus be lost when vomiting occurs or when gastric suction is applied Changes in total body potassium result from the balance of the factors outlined above but in a given period there might also have been breakdown of tissue with the release of potassium or synthesis with its absorption Thus in order to get an idea of the significance of changes in body potassium so far as living tissue is concerned it is necessary also to know the nitrogen balance over the same period Since the normal ratio of potassium to nitrogen in protoplasm is known the crude potassium balance can be corrected by deducting the change in potassium which should have occurred as a normal accompaniment of the change in body nitrogen (*b*) The size of the potassium ion in watery solution is relatively small (a good deal smaller than sodium) and according to the theory of Conway and Boyle (1939) it is freely diffusable across a cell membrane Chloride ion is also freely diffusable but the cell membrane is relatively impermeable to sodium Conway and Boyle by a consideration of thermodynamic principles explain on this basis the relative positions of the various ions on either side of the cell membrane As might be expected therefore when some ionic change occurs in the extracellular compartment potassium may flow in one or other direction across the cell membrane It has been shown by Darrow (1946 1950) that a rise in extracellular bicarbonate level is always accompanied by a fall in intracellular potassium provided the kidney can excrete the potassium which moves out of the cells Dehydration particularly that associated with an increase in the osmotic pressure of body fluids is also associated with a transfer of potassium from cells to extra

cellular fluid and thence to the urine On the other hand it is probable that a certain proportion of the cellular potassium is absorbed on to protein and that the proportion can change such changes being associated with a transfer across the cell membrane The movement of potassium is also intimately associated with carbohydrate metabolism, potassium moving in to the cells whenever carbohydrate metabolism is taking place (Fenn, 1940) This is a possible explanation of why the paralytic episodes in Familial Periodic Paralysis can be precipitated by a high carbohydrate meal or by injections of glucose or insulin The stimulation of carbohydrate metabolism causes a rapid transfer of potassium into the cells and thus lowers the concentration in the extracellular fluid to levels which result in muscular paralysis The fall in serum potassium seen after commencement of treatment of diabetic coma is probably brought about in part by a similar mechanism

Finally the adrenal cortex is concerned in potassium regulation an increase in function resulting in loss of potassium from the cells and body and a decrease resulting in retention One of the effects of overdosage with D O C A is potassium deficiency with, in extreme cases muscular paralysis (Hollingsworth 1949) and it is possible that the potassium loss which has been observed to follow operation is associated with adrenal cortical hyperfunction following the operative stress

Most cases of potassium deficiency do not appear to have specific signs or symptoms Certain abnormalities however frequently accompany potassium deficiency and clear up remarkably quickly when adequate amounts of potassium are given It is not at all certain whether intracellular potassium defect *per se* can give rise to any clinical abnormalities or whether a lowering of extracellular potassium is necessary before they are produced It does seem, however that the most specific clinical signs of potassium defect those of muscular weakness and changes in the electrocardiogram are invariably associated with low serum levels although there is no precise level below which they are found It is the experience of the author that voluntary muscle paralysis is always preceded by electrocardiographic changes and that the latter changes are not infrequently found whereas paralysis of voluntary muscles is comparatively rare Figs 6 & 7 show the typical E C G changes in a case of potassium deficiency before and after treatment The changes which occur may become manifest at a serum potassium level of about 3 m Eq /litre (11 7 mgms per 100 ml) or less They consist of a slight prolongation of the QT interval in relation to the corresponding PT interval a decrease in the height and a prolongation of the T wave which may merge with the succeeding P a depression of the ST segment possible inversion of the P wave extra systoles and auriculo ventricular block In addition there seems to

be some variability in the exact shape of the ventricular complex (Figures 6 and 7)

When voluntary muscle paralysis occurs the respiratory muscles are the last to be affected It is unusual to see paralysis in cases of potassium deficiency but when it does occur it is usually seen in patients who are recovering from diabetic coma in subjects with renal lesions

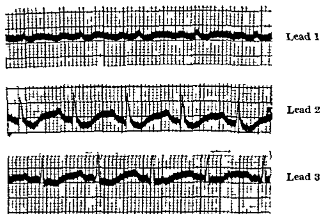


FIG 6 ECG changes associated with low levels of serum potassium in a case of nephrocalcinosis The serum potassium was 2 0 m Eq per litre (7 8 mg per 100 ml)

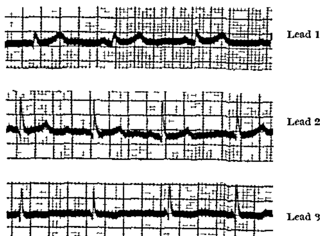


FIG 7 ECG changes in the same patient when the serum potassium level had been adjusted to 4 9 m Eq per litre (19 2 mg per 100 ml)

cellular fluid and thence to the urine On the other hand it is probable that a certain proportion of the cellular potassium is absorbed on to protein and that the proportion can change, such changes being associated with a transfer across the cell membrane The movement of potassium is also intimately associated with carbohydrate metabolism potassium moving in to the cells whenever carbohydrate metabolism is taking place (Fenn, 1940) This is a possible explanation of why the paralytic episodes in Familial Periodic Paralysis can be precipitated by a high carbohydrate meal or by injections of glucose or insulin The stimulation of carbohydrate metabolism causes a rapid transfer of potassium into the cells and thus lowers the concentration in the extracellular fluid to levels which result in muscular paralysis The fall in serum potassium seen after commencement of treatment of diabetic coma is probably brought about in part by a similar mechanism

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(1) If potassium can be given by mouth this is the best route The relatively slow absorption renders this route practically harmless if there is an adequate urinary flow

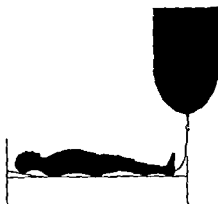


Fig 8 Showing the relative volumes of total body and Hartmann's solution required to replace deficient potassium in an average case

(2) Potassium should never be given without the strictest biochemical control when there is oliguria or anuria

(3) If potassium is given parenterally it must be given as a slow drip there should be not more than 25 m Eq (1 g) of potassium per litre and this should never be given in less than one hour Not more than three such amounts should be given in 24 hours since greater quantities are not retained (Darrow 1950)

(4) If a flame photometer is not available so that rapid estimations of serum potassium are not possible and if it is feared that toxic levels may be reached then electrocardiographic changes should be followed These will always precede any dangerous clinical alterations in the heart action and will give due warning that toxic levels have been reached Indeed it may well be that E C G changes are a more reliable index of the *clinical* state of the patient than a biochemical estimation of the serum potassium level (Merrill Levine Somerville and Smith 1950) Typical changes are in the first place an increase in the voltage of the T waves which become tall and pointed next a straightening out of the S T segment so that the curve runs almost straight from the bottom of the S wave to that of the T wave These changes are seen in Figures 9 and 10 Prolongation of the P R interval next occurs with diminution in the voltage of the P wave and finally auricular arrest Next the voltage of the R wave increases and the duration of the ventricular complex increases as does the depth of the S waves until all normal

such as chronic nephritis or so called nephrocalcinosis or, much more rarely, in subjects with sprue and in patients with Addison s disease who have received too much D O C A The characteristic features are similar to those seen in familial periodic paralysis

Other clinical accompaniments of potassium deficiency are lassitude or listlessness, anorexia, intestinal ileus, at times diarrhoea and peripheral oedema Biochemically there may be low serum chlorides and alkalosis which will not improve however much saline is given until the potassium defect is corrected The giving of large quantities of saline intravenously will often in fact aggravate the deficiency since the kidneys excrete greater amounts of potassium under these conditions The condition par excellence in which potassium defect occurs is the post operative patient having continuous gastric suction and intravenous saline and glucose In such a case (1) there is no potassium intake (2) there is adequate urinary output with consequent potassium loss (3) there is alkalosis (4) there is the usual post operative loss associated with stress, (5) the glucose may stimulate cellular carbohydrate metabolism and lower still further the extracellular potassium

To summarize potassium deficiency should be considered whenever the intake is deficient and urinary output is maintained whenever alkalosis is present whenever there is dehydration whenever large quantities of body fluids are lost and have been replaced by physiological saline and/or glucose solutions in most shocked and in many post operative patients As described under Diabetes', potassium deficiency can be assumed to be invariably present when cases of diabetic coma are under treatment Deficiency should be suspected in patients with chronic renal disease with so called base losing nephritis and with amino aciduria as well as in cases with severe diarrhoea such as sprue and ulcerative colitis

The Treatment of Potassium Deficiency

It has been found that patients suffering from the disorders outlined above may have lost as much as 10 m Eq (390 mg) potassium per kilogram body weight If normal extracellular fluid were used to correct such a deficit it would be necessary to give about twice the volume of the whole patient and thus would entail giving about 30 times as much sodium and chloride as necessary The futility of relying on physiological solutions such as Hartmann s to correct the potassium defect can thus be realised and is illustrated diagrammatically in Figure 8

Nevertheless potassium is highly toxic if the level in the extracellular fluid becomes too high and cessation of the heart beat may occur even when only temporary local toxic concentrations are reached The following rules should therefore be adopted —

begin at a serum potassium level of 7–8 m Eq /1 (28–31mg / 100 ml) and death may occur at about 12 m Eq /1 (35 mg / 100 ml)

Intoxication due to overdosage should be treated by the administration of intravenous calcium gluconate and sodium chloride since the effect of potassium ion is to some extent antagonised by calcium and sodium In addition glucose and insulin which results in the removal of some of the extracellular potassium into cells should be given If potassium intoxication occurs in association with anuria it may be necessary to undertake peritoneal dialysis

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THE USE OF ISOTOPFS (See also Chapter II)

General Consideration An element has two parameters by which it may be defined the atomic number (the number of protons in the nucleus of the atom) and the atomic mass (in round figures the total number of protons and neutrons in the nucleus) The atomic number determines the chemical properties and elements of different atomic mass and similar atomic number are isotopic Atoms may be stable or unstable depending upon a somewhat complicated relationship of mass and atomic number

Stable isotopes are in general estimated by methods which are involved and tedious whereas the particles emitted by unstable isotopes can usually be measured by suitable and relatively simple apparatus On the other hand the radioactive isotopes may be highly toxic because of their radiations β and γ particles are the emissions from radioactive elements which are most generally used in medicine The range of β particles depends largely upon the density of the substance through which they are passing and upon the energy with which they are emitted this being a characteristic property of the particular

contour is lost and the ventricular complex assumes a "saw tooth" appearance. Ventricular arrhythmias may then appear and finally ventricular arrest.

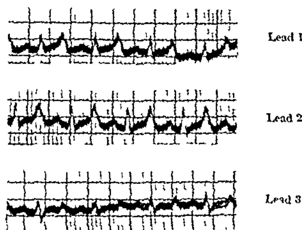


Fig 9. E.C.G. changes associated with potassium intoxication in a case of anuria. The serum potassium was 8·[illegible] m.Eq. per litre (32 mg. per 100 ml.)

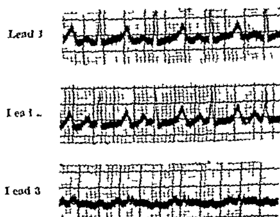


Fig. 10. E.C.G. changes in the same patient when the serum potassium had fallen to [illegible] m.Eq. per litre (21·5 mg. per 100 ml.)

The changes are only roughly related to the level of serum potassium and are accentuated for a given potassium level if the serum sodium is low. In very rough terms they may

neoplasms to a greater extent than in the surrounding tissues This fact has been used by Moore (1947) and Boyack *et al* (1948) to develop a method for the diagnosis and localisation of cerebral tumours Fluorescein is the dyestuff used and I^{131} is incorporated in the molecule to give radioactive diiodofluorescein This substance is then injected and is concentrated in and around cerebral neoplasms from 2–17 times more than in the surrounding cerebral tissue The γ particles emitted from the I^{131} are counted at the surface of the skull the counts at corresponding points on either hemisphere being compared Davis and co workers (1950) have recently reviewed the use of this method in 200 cases of suspected cerebral neoplasm and compared the results with subsequent post mortem or operative findings and with the results of electro encephalographic examination and ventriculography on the same patients Much more accurate diagnosis was possible than by either of the latter two methods Of 95 patients with *subsequently confirmed space occupying lesions in only four were* completely erroneous results obtained in only one case was dye so concentrated as to simulate a tumour when in fact none was present The test is rapidly carried out is no more unpleasant to the patient than any intravenous injection and does not entail any appreciable hazard from irradiation

It has been found that phosphorus accumulates in greater quantities in cerebral neoplasms than in the surrounding tissue and this fact has been utilised by Selverstone Solomon and Sweet (1949) who have administered P^{32} to patients about to be operated upon for cerebral neoplasms This isotope on decay emits a β particle and no γ particles Counting at the surface would not therefore yield any useful information The authors however developed a very small probe counter which could be inserted into the brain substance at operation and by which they were better able to delineate the neoplasm

Therapeutic Uses Radioactive iodine has been used with much success in the treatment of hyperthyroidism both I^{131} with a half life of eight days and I^{130} with a half life of 12 6 hours having been used Details of this use are given in Chapter X

Apart from the accumulation of injected P^{3} in neoplastic tissue as already mentioned this isotope following the route of naturally occurring P^{31} is deposited to a very great extent in bone For this reason P^{3} has been used in the treatment of leukæmias and multiple myeloma (Warren 1945 a and b) and in polycythæmia vera (Hall *et al* 1945) One can conclude that it is a very useful therapeutic agent for cases of polycythæmia vera but that little more than temporary remission can be expected to follow its use in leukæmia although it is probably a more convenient means of irradiation than conventional deep X ray therapy

isotope from which they are derived In body tissues this range is usually not more than a few millimetres γ particles also have a range determined by their energy and by the substances through which they are passing but their penetrating power is relatively very high When these particles traverse the tissues they cause ionisation and upon this depends the biological effect Similarly, the detection and subsequent counting of these particles depends upon their ability to produce ionisation in the counting chamber

The particular particles emitted and the mean energies of these particles is a characteristic of each radioactive isotope and a further fundamental property is that each and every atom of a given isotope is equally liable to disintegrate within a given time the likelihood of this occurring also being a characteristic unique to each isotope If activity be defined as the number of disintegrations occurring *per second* it *can thus be seen that the activity of a given isotope sample will fall off geometrically* i e *the time taken for the activity to decrease by half will always remain the same* This period of time is called the half life and is a characteristic constant of each individual radioactive isotope

Stable isotopes particularly deuterium and heavy carbon have been and are being used in research but the technical difficulties are great so that there have not been any immediate uses in clinical medicine Consideration will therefore only be given to the radioactive isotopes

Radioactive isotopes are being used in medicine for three main purposes research diagnosis and therapy Their use for research purposes is often elegant and highly fruitful but it is not proposed to deal with this aspect except to point out that this is undoubtedly the field wherein their use has yielded the greatest returns particularly in elucidating various aspects of metabolism

Diagnostic Uses One method of utilising radioactive isotopes is to use an isotope of an element which is concentrated specifically by the particular part of the body under study The best example of this is the use of radioactive iodine in the study of thyroid function

Iodine is concentrated in the thyroid to a much greater extent than in other tissues and the extent to which it is taken up can be measured by counting the γ particles at the surface of the skin over the thyroid Details of the methods which have been evolved for this purpose are given in Chapter X

Another method whereby radioactive isotopes can be used for diagnosis is to incorporate a suitable unstable isotope in a compound which is concentrated in the tissue or organ under consideration For example it has been shown that capillaries of most neoplasms are more permeable to certain dyestuffs than normal capillaries (*Ludford* 1929) These substances are thereby concentrated in and around

in Castle's intrinsic factor (Berk *et al* 1948) Also the fæces of patients suffering from pernicious anæmia contain large quantities of B_{12} (Dyke *et al* 1950) and it seems that the most likely explanation of the facts known at present is that vitamin B_1 Castle's extrinsic factor and anti anæmic principle are all similar substances Castle's intrinsic factor being necessary for the adequate absorption of B_{12} from the alimentary tract Anti anæmic principle may be a conjugation of B_{12} and intrinsic factor but if so there must be other sources than the alimentary tract of intrinsic factor in the body

Although it now seems fairly certain that the key metabolic factor in pernicious anæmia is vitamin B_{12} or a closely related substance this is by no means the case in many other types of macrocytic anæmia Although there have been some controversial results it seems that vitamin B_{12} is frequently ineffective or only slightly effective in cases of so called pernicious anæmia of pregnancy and in cases of macrocytic anæmia associated with steatorrhea or in anæmia following gastrectomy (Ungley and Thompson 1950 Patel and Kocher 1950 Conway and Conway 1951) In such cases the administration of folic acid by mouth is fully effective and this therapy does not seem to precipitate neurological lesions (Girdwood 1950)

Various substances closely related to vitamin B_{12} all of similar chemical formula and all containing cobalt have been obtained from different sources or by chemical modifications They have been labelled B_{12a} B_{12b} B_{12c} B_{12d} (Smith 1951 Ungley and Campbell 1951)

Although some preparations of B_{12} are still obtained from liver the greatest source is from the synthesis of this vitamin by streptomyces griseus Therapeutically all the B_{12} analogues have similar actions The isolation of vitamin B_1 has made it obvious that the previously accepted mechanism for the production of pernicious anæmia must be considerably modified but sufficient facts are not yet available for the adequate synthesis of a new hypothesis

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FOLIC ACID AND VITAMIN B12

Since the discovery that folic acid in daily doses of about 2 5 mgm will cause the rapid remission of most cases of megalocytic anæmia including pernicious anæmia there has been much renewed interest in the factors involved in normal hæmopoiesis Particularly intriguing and important were the facts that active liver extracts contained little or no folic acid and that folic acid when given to patients suffering from pernicious anæmia not only did not cure any neurological lesions which might be present but might even precipitate such lesions (Israels and Wilkinson 1949) The isolation of vitamin B_{12} independently and almost simultaneously in America and England (Rickes *et al*, 1948 Lester Smith 1948) has marked a further very important step forward It is evident that vitamin B_{12} in parenteral doses of only a few micrograms will cause a considerable hæmopoietic response in cases of pernicious anæmia and that the neurological lesions the glossitis and the general feelings of lassitude and malaise associated with pernicious anæmia are also all relieved by B_{12} given parenterally Very satisfactory results are obtained from doses of the order of 50 µg every other week (Ungley 1949a 1949b) In addition neurological lesions precipitated by folic acid may be beneficially affected by B_{12} (Fuld 1950)

Whereas folic acid is effective in stimulating hæmopoiesis when given by mouth vitamin B_{12} is quite ineffective orally unless given in doses about one hundred times as great as are necessary parenterally Smaller doses are effective however if they are accompanied by normal gastric juice or by stomach preparations known to be rich

sex hormones and vitamin C are necessary for the maintenance of normal osteoblastic activity and an adequate protein intake is necessary to provide the raw material for the laying down of organic matrix by osteoblasts Thus as has been well known for years osteoporosis occurs in scurvy Most commonly however the condition is seen in post menopausal women and in the senile of both sexes almost certainly as a result of deficient œstrogens or androgens (Anderson 1950b) It is also seen from the same cause in ovarian agenesis in Klinefelter s syndrome in eunuchoidism and in hypopituitarism Osteoporosis occurring in acromegaly is also probably secondary to the hypogonadism so frequently present in this condition at all events it responds to the exhibition of sex hormones Malnutrition may result in osteoporosis as a result of the poor protein intake and it is possible that a similar state of affairs may occur secondary to hyperthyroidism and to long standing poorly treated diabetes mellitus Excessive outpouring of the gluco corticoids from the adrenal cortex such as is seen in Cushing s syndrome or in prolonged stress also results in osteoporosis probably because of the catabolic effect of these hormones on tissue protein The inherited defect of mesenchymal tissue osteogenesis imperfecta also results in osteoporosis In this condition the osteoblasts are probably if anything more active than normal but they fail to lay down an adequate organic matrix Finally a few cases of osteoporosis have been reported where none of the above factors appeared to be involved

Clinically osteoporosis most frequently affects the vertebræ and pelvis and the post menopausal and senile types are the most frequently seen It is as would be expected more common in women than in men It may be entirely symptomless but there may be pain in the back varying from a slight ache to one of great severity There is usually a gradually increasing kyphosis and frequently the vertebral bodies become narrowed and biconcave from pressure of the inter vertebral discs which become enlarged Collapse of the vertebral body may occur and even this may only be found incidentally at an X ray examination for some other condition If osteoporosis occurs from lack of sex hormones before the epiphyses are united as in the congenital conditions outlined above there is delayed union of the epiphyses and this gives rise to the deformity of so called epiphysitis in addition to the osteoporosis Albright points out that the lamina dura round the teeth always remains intact in osteoporosis and that in difficult cases this may be an important point of differentiation from generalised osteitis fibrosa cystica Biochemically the serum calcium is normal and so usually is the serum phosphate though this may be slightly raised in the post menopausal group The serum alkaline phosphatase is also normal

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METABOLIC BONE DISEASE

Osteoporosis and Osteomalacia

The valuable and illuminating work carried out on bone metabolism under the direction of Fuller Albright has recently been summarised (Albright and Reifenstein 1948)

These authors emphasise that demineralisation of bone can occur either as a result of atrophy of the organic matrix or as a result of some defect in calcium or phosphate metabolism osteoporosis is used strictly for the former and osteomalacia for the latter set of conditions A further point of emphasis of great importance is that stress and strain are potent stimuli to osteoblastic activity and that osteoblasts are the source of the high serum alkaline phosphatase levels found in so many bone diseases The level of serum alkaline phosphatase taken in conjunction with the amount of diseased bone, affords in the absence of liver disease some indication of osteoblastic activity for example of all bone diseases active Paget s disease in which there is tremendous osteoblastic activity has the highest serum alkaline phosphatase level per unit of bone involved

Osteoporosis This can result from local causes as in disuse atrophy where lack of movement whether resulting from splinting or from local disease diminishes the normal mechanical stresses and strains present in the bones and so decreases osteoblastic activity below normal In normal bone there is a continuous loss of the mineral elements and simultaneously a continuous mineral deposition by means of osteoblastic activity Therefore disuse with resultant diminished osteoblastic activity will inevitably result in some loss of minerals from the bone

Osteoporosis from general causes occurs as the result of lack of the normal physiological stimuli to osteoblastic activity from lack of the nutritional elements required to lay down organic bony matrix or from excessive breakdown of the organic framework of bone The

pseudo fractures (iv) Gross skeletal demineralisation apparent radiologically

Osteomalacia may result from deficient intake or absorption of calcium or phosphate as a dietary defect secondary to deficiency of vitamin D or secondary to steatorrhœa Resistance to vitamin D may also result in osteomalacia very large doses being necessary in such cases to produce a cure Osteomalacia may also result from excessive calcium loss in the urine such as occurs in renal acidosis resulting from so called nephrocalcinosis from the congenital tubular defect described by Fanconi (1936) or from cases of idiopathic hypercalcuria in which there is excessive renal loss of calcium without acidosis and with normal or low serum calcium levels In Albright s view, renal rickets resulting from total deficiency of renal function is quite distinct from osteomalacia and is in reality osteitis fibrosa cystica secondary to parathyroid hyperplasia

Treatment of osteomalacia must obviously be related to the cause Nutritional defect and lack of or resistance to vitamin D are easily rectified the usual remedies should be applied to cases of steatorrhœa Osteomalacia resulting from nephrocalcinosis is dramatically relieved by the giving of alkalis It should be noted however that potassium deficiency not infrequently occurs in this syndrome and in this event potassium should be included in the alkaline salts administered The citrates are usually given and 5–15 grams per day may be necessary to relieve the condition It is perhaps fortunate that idiopathic hypercalcuria rarely produces gross osteomalacia since therapy by means of a high calcium intake and adequate amounts of vitamin D though curing the osteomalacia may result in the increased formation of renal calculi

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Treatment of osteoporosis should be directed to the cause In the vast majority of cases this is the inadequate stimulation of osteoblastic activity by the appropriate sex hormones and stilbœstrol and testosterone are very *effective in ameliorating the condition About* 1 mg per day of diethyl stilbœstrol is fully effective but it may take as long as 30 days before the results of this therapy become maximal *no effects can be detected before* about one week This therapy should be interrupted for about one week in every five in order to prevent the development of metropathia Testosterone compounds may also be given to females provided they do not produce too much masculinisation A dose of 10 or 20 mg of methyl testosterone per day by mouth is usually effective Oedema may be produced in old people by this therapy, in which case they should also receive a low sodium diet Although patients so treated improve remarkably and soon become symptom free and although balance studies show considerable calcium and phosphate retention it takes a very considerable time before any convincing increase in bony calcification occurs as judged from the X ray picture

Osteomalacia Osteomalacia being defined as that condition resulting from the failure of calcium salts to be deposited in newly formed organic matrix, it is essential that the solubility product of ionic serum calcium and phosphate is too low to permit local precipitation of the calcium phosphate carbonate complex by osteoblasts Thus biochemically one may find a low serum calcium with normal phosphate a low phosphate with normal calcium or low calcium and low phosphate Since resorption of bone continues at normal or *increased rates this may* eventually lead to definite weakening of the bony structure with the resultant increase in stresses and strains acting as a strong stimulus to osteoblastic activity This increased activity *is reflected by an increased level of serum alkaline phosphatase* The decalcification and bony weakness may result in so called pseudo fractures before there is any definite X ray evidence of generalised *increased translucency*

The fractures characteristically affect the cortex of the bone may be symmetrical and look on the X ray like faint wedge shaped zones of translucency *Histologically there is a large amount of* decalcified callus present They have been described by Looser (1920) and by Milkman (1930) and Albright *et al* (1946) regard them as a characteristic feature of *osteomalacia Finally the decalcification of the* skeleton may become obvious on X ray examination Osteomalacia is thus divided by Albright and his colleagues into the four stages (i) Low serum calcium and/or *phosphate with normal alkaline phosphatase* (ii) Low serum calcium and/or phosphate with high alkaline phosphatase (iii) The chemical changes of (ii) together with X ray evidence of

D Single ventricle —
(1) with pulmonary artery arising from a rudimentary outlet chamber
(2) with pulmonary stenosis
E Transposition of the great vessels with pulmonary stenosis
F Patent foramen ovale with pulmonary stenosis
G Ebstein s disease with patent foramen ovale
H Anomalous venous return —
(1) pulmonary arteriovenous fistula
(2) superior vena cava emptying into the left auricle

II Pulmonary Flow greater than Systemic Flow and/or Pulmonary Artery Pressure Normal or Increased
A Eisenmenger s complex
B Transposition of the great vessels —
(1) complete
(2) partial
C Isolated septal defect —
(1) auricular septal defect
(*a*) uncomplicated
(*b*) Lutembacher s disease
(2) ventricular septal defect
D Aortic atresia with patent ductus arteriosus
E Single ventricle —
(1) with both great vessels arising from the rudimentary outlet chamber
(2) with the aorta arising from the rudimentary outlet chamber
F Truncus arteriosus
G Patent ductus arteriosus
H Anomalous venous return with pulmonary veins emptying into the vena cava or the right auricle

III Pulmonary Flow Equals the Systemic Flow at Rest and After Exercise
A Pure pulmonary stenosis
B Patent foramen ovale as an isolated anomaly
C Coarctation of the aorta —
(1) adult type
(2) infantile type without patent ductus arteriosus
D Double aortic arch

Surgery can correct patent ductus arteriosus coarctation of the aorta (adult type) double aortic arch and pulmonary arteriovenous fistula It can improve the tetralogy of Fallot tricuspid atresia pseudotruncus arteriosus single ventricle with inadequate pulmonary blood flow (ID) and pulmonary stenosis with patency of the foramen

CHAPTER V

CARDIOVASCULAR DISEASES

by

RAYMOND DALEY

with a section on

ELECTROCARDIOGRAPHY

by

M B MATTHEWS

Congenital heart disease Treatment of myocardial infarction by anticoagulants Rheumatic fever Pulmonary hypertension Pheochromocytoma The Collagen diseases Polyarteritis nodosa Disseminated lupus erythematosus Dermatomyositis Scleroderma

CONGENITAL HEART DISEASE

THERE are many classifications of congenital heart disease based on anatomical grounds on the presence or absence of cyanosis and on altered hæmodynamics The last has the advantage of having more application to the possible surgical correction of various lesions The following classification is after Bing (1949)

Table III
Classification

I Pulmonary Flow less than Systemic Flow Pulmonary Artery Pressure Usually Decreased
- A Tetralogy of Fallot
- B Pseudotruncus arteriosus
- C Tricuspid atresia

of blood from various regions is analysed and especially is this so if the aorta and pulmonary artery are entered It is though of particular value in enabling calculations to be made of the pulmonary and systemic arterial flows and the effective pulmonary blood flow The calculations are made as follows according to the Fick principle (after Bing) —

Pulmonary arterial blood flow = O uptake in c c s per minute / O content of blood in the pulmonary vein—O content of blood in the pulmonary artery (vols per cent) × 100/1

Systemic arterial blood flow = O uptake in c c s per minute / O content of blood in a systemic artery—O content of mixed venous blood (vol per cent) × 100/1

Effective pulmonary blood flow = O uptake in c c s per minute / O content of blood in the pulmonary vein—O content of mixed venous blood (vols per cent) × 100/1

These calculations are only approximations and pulmonary venous blood is assumed to be 98 per cent saturated

The concept of effective pulmonary blood flow (Bing *et al* 1947) meaning the volume flow of blood which after its return to the right auricle ultimately reaches the pulmonary alveoli is useful in enabling the following calculations of shunts to be made —

Right to left shunt = pulmonary artery blood flow minus effective pulmonary blood flow

Left to right shunt = systemic pulmonary blood flow minus effective pulmonary blood flow

In the tetralogy of Fallot the effective pulmonary blood flow is low and the shunt predominantly right to left Treatment consists in increasing the effective pulmonary flow by a Blalock (1946) type of anastomosis usually the right subclavian artery to the right pulmonary artery (if the aortic arch is on the left) or a Potts (1948) anastomosis between the aorta and pulmonary artery or removal of the obstruction to the outflow from the right ventricle (Brock 1948) The pulmonary stenosis is usually infundibular and may be relieved by resection of part of it

The results of all these procedures are good and which is done mainly depends upon the preference of the surgeon Blalock has now the largest series and Taussig *et al* (1950) recently analysed the results of 716 patients suffering from Fallot s tetralogy who were operated on by him The mortality was 19 per cent Of those who were greatly benefited by operation over 80 per cent are doing well six months to five years later

ovale It is still experimental in the closure of auricular and ventricular septal defects, in the creation of auricular septal defects as in transposition of the great vessels and in the transplanting of great veins from one side of the heart to the other as in transposition and in various anomalies of venous return

It is proposed here to discuss the diagnosis and treatment of those lesions which have inadequate pulmonary blood flow and which can be improved by surgery

The Tetralogy of Fallot

The tetralogy consists of pulmonary stenosis or atresia dextro position of the aorta a high interventricular septal defect and right ventricular hypertrophy It is the most common form of cyanotic congenital heart disease Cyanosis is either present at birth or develops fairly shortly afterwards and sometimes becomes much worse when the ductus closes which is usually delayed until between 6 and 18 months of age Clubbing is marked Dyspnœa is present from an early age and squatting on the haunches after exercise is common Growth is impaired but intelligence as opposed to educational opportunity is normal as in other forms of cyanotic congenital heart disease "Congestive attacks in which a child becomes very cyanotic dyspnœic and even unconscious are common and are believed to be due to an increase in the right to left shunt consequent upon a decreased systemic arterial resistance They are helped by oxygen inhalation and morphine

There is sometimes enlargement of the left chest and elevation of the left nipple due to right ventricular enlargement (not to be confused with scoliotic chest deformity) There is usually a systolic murmur heard down the left sternal border but this may be absent in pulmonary atresia and replaced by a continuous murmur heard over most of the chest due to bronchial collateral blood flow The second sound is single and sometimes a little louder than normal due to the proximity of the aorta to the chest wall

Fluoroscopy shows the right ventricle to be enlarged the pulmonary artery shadow slight or absent and vascular markings in the lungs decreased In about 20 per cent of patients the aortic arch is on the right Angiocardiography is a useful diagnostic aid and shows simultaneous filling of the aorta and pulmonary artery (if there is pulmonary stenosis and not atresia) but it has the further advantage of showing the approximate size of the main pulmonary arteries and the position of the innominate and subclavian arteries which might be used for an anastomotic operation Cardiac catheterisation is of diagnostic help if pressure records are taken and the oxygen content

Single Ventricle with Rudimentary Outlet Chamber

In this condition there is a muscular ridge guarding the rudimentary chamber which lies in the region of the pulmonary conus If the aorta arises from this chamber the child will be under-developed but the lungs being supplied by a pulmonary artery arising from the main chamber will be well vascularised If both great vessels arise from the chamber there will be both under development and inadequate pulmonary blood flow Here will be discussed the situation in which the pulmonary artery arises from the rudimentary chamber and the aorta from the main chamber

Cyanosis and dyspnœa are severe On fluoroscopy the lungs are clear the rudimentary chamber shows as a prominence in the region of the pulmonary conus and there is insignificant enlargement of the right ventricle in the left anterior oblique position The condition is distinguished from tricuspid atresia both by the shadow cast by the rudimentary chamber and right not left axis deviation in the electro cardiogram

Catheterisation may suggest the diagnosis if the oxygen content of blood in the right ventricle is much higher than in the right auricle Anastomotic operations are theoretically advantageous but the mortality is very high

Pulmonary Stenosis with Patency of the Foramen Ovale

In this malformation the pulmonary stenosis is nearly always valvular and the foramen ovale remains patent Clinically there is marked dyspnœa and cyanosis develops after birth The right heart becomes much enlarged and often leads to enlargement of the left chest The right ventricular and auricular pressures are high and there is often a pronounced a wave in the jugular venous pulse with in some instances a pulsating liver There is usually a pulmonary systolic murmur and in the pulmonary area a single weak second sound The fluoroscopic appearances are those of an enlarged right heart with vigorous auricular pulsation post stenotic dilatation of the pulmonary artery and poorly seen peripheral vascular lung markings The electrocardiogram confirms the right ventricular enlargement but there may also be tall P waves and a prolonged PR interval On catheterisation there is a low pulmonary artery pressure and high right ventricular and auricular pressures Angiocardiography shows delay in filling the pulmonary artery and the aorta may be filled via the patent foramen ovale the left auricle and left ventricle

Anastomotic operations in such patients may cause temporary improvement if the foramen ovale subsequently closes but right heart failure usually results The Brock (1948) type of pulmonary

Tricuspid Atresia

When there is atresia of the tricuspid valve there is under development of the right ventricle and either an auricular septal defect or patency of the foramen ovale Blood usually reaches the lungs via an interventricular septal defect and the diminutive right ventricle but it may do so by the aorta and a patent ductus arteriosus or by bronchial arteries

The symptoms and signs are similar to those of Fallot s tetralogy Radiologically, however, in the anteroposterior view the pulmonary artery area is concave but the left ventricle is enlarged In the left anterior oblique position the diminutive right ventricle does not project beyond the line of the aorta Electrocardiographically it is the only form of cyanotic congenital heart disease with left axis deviation (excluding dextrocardia) The diagnosis should be made on these findings and while angiocardiography may confirm it catheterisation is of little help

Treatment is either by a Blalock or Potts type of anastomosis Taussig *et al* (1950) reports that with the Blalock type of anastomosis the over all mortality was 33 per cent

Pseudotruncus Arteriosus

In truncus arteriosus a large vessel over rides both ventricles and there is a ventricular septal defect and right ventricular hypertrophy In true truncus arteriosus the pulmonary arteries arise from this main trunk and *as the pulmonary blood flow is quite good disability is not* great In pseudotruncus arteriosus there are no pulmonary arteries arising from the main trunk and the lungs are supplied by bronchial *collateral vessels or via a patent ductus and the pulmonary arteries* In this disease cyanosis and disability from birth are severe Taussig and Cohen (1950) have laid down the following five most important *diagnostic signs* —

(1) A continuous murmur from collateral pulmonary blood vessels
(2) A prominent aortic knob
(3) Absence of the normal shadow cast by the pulmonary arteries
(4) Anomalous retro œsophageal vessels distorting the barium filled œsophagus
(5) Some degree of oxygen unsaturation of arterial blood

Angiocardiography offers the best aid in diagnosis If there are pulmonary arteries and the pressure is low within them a Blalock anastomosis is possible but if they are absent an attempt may be made still further to increase the collateral blood flow to the lungs by stripping the parietal pleura and encouraging the growth of vascular pleural adhesions (Barrett and Daley 1948)

in the first two months are cardiac failure with or without further myocardial infarction pulmonary infarction and peripheral arterial embolism Hellerstein and Martin (1947) found that 11 5 per cent of patients with myocardial infarction developed clinical evidence of thrombosis or embolism

What then can be done to improve these mortality figures with anti coagulant drugs? *Wright et al (1948) in a very large and well con* trolled series of patients reduced the mortality from 24 to 15 per cent largely by decreasing the number of thrombo embolic complications Tulloch and Gilchrist (1950) found that anticoagulant therapy halved the mortality rate during the first six weeks following myocardial infarction and thrombo embolic complications were reduced by the same amount

The complications of anticoagulant therapy are well known and in the absence of safer drugs than are at present available treatment must be carried out in hospital and should be continued for three to four weeks The scheme of dosage for Heparin and Dicoumarol is outlined in the previous edition (pp 148 149) Heparin remains a safe anticoagulant but of course has the disadvantages of having to be injected and of expense It should still be used at the start of treatment if Dicoumarol is also to be used but other anticoagulants such as Tromexan [bis 3 3[1] (4 oxycoumarinyl) ethyl acetate] (in oral doses of 0 9 to 1 2 grammes for the first two days and then 0 3 to 0 6 gramme daily depending on the prothrombin time) may well replace Dicoumarol because it is effective within 36 hours of adminis tration its main effect passes off in the same time (Burt *et al* 1949) and hæmorrhagic complications are relatively uncommon

Thus there is considerable evidence that anticoagulant therapy should be given to patients as soon as possible following myocardial infarction and it can reasonably be expected to lessen the dangers of pulmonary and systemic embolism and recurrent coronary thrombosis

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valvulotomy is the only known form of satisfactory operation and the results may be very good pulmonary regurgitation rarely being produced

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THE TREATMENT OF MYOCARDIAL INFARCTION BY ANTICOAGULANTS

Occlusion of a coronary artery by thrombosis is not necessarily followed by myocardial infarction and myocardial infarction sometimes occurs without coronary occlusion Hence myocardial infarction should be diagnosed when there is evidence of dead muscle i e large broad Q waves in the electrocardiogram fever leucocytosis and a raised erythrocyte sedimentation rate

The mortality figures for myocardial infarction are difficult to assess but under the usual therapeutic regime of morphia bed rest and oxygen inhalation (which presumably raises tissue oxygen tension) certain facts can be stated with some certainty There is a real increase in deaths from myocardial infarction (Ryle and Russell 1949) Apart from patients who die before being admitted to hospital about a quarter will die within the first two months, about half by the end of a year about two thirds by the end of the third year and about four fifths by the end of five years (Katz et al 1949) In men under 40 years of age a very careful analysis by Yater and his colleagues (1948) has shown that 31 per cent died within two hours of the onset of infarction and a further 18 per cent died within 24 hours Similar figures are not available for older patients but it is probable that a higher proportion survive sufficiently long for them to be treated in hospital

The crude mortality rate for hospital patients without any specific treatment is in the region of 30 to 40 per cent The modes of death

in the first two months are cardiac failure with or without further myocardial infarction pulmonary infarction and peripheral arterial embolism Hellerstein and Martin (1947) found that 11 5 per cent of patients with myocardial infarction developed clinical evidence of thrombosis or embolism

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RHEUMATIC FEVER

Rheumatic fever occurs in every country in which it has been sought *although it is much more common in northern countries with cold* damp climates It has a maximal incidence in the spring and autumn and is especially common in over crowded poverty stricken areas *The disease is a little more frequent* in females than males and the greatest incidence of first attacks is between five and ten years of age First attacks after the age of 20 are rare but recurrences or " reactivation " *of previous rheumatic carditis may occur at any age and there* are an increasing number of reports of active rheumatism in the very elderly

The infective theories of ætiology *of acute rheumatism remain* unclear The virus theory of Schlesinger and others has now largely been superseded by the streptococcal theory It is well known that outbreaks of upper respiratory tract infection are followed by an increased incidence of acute rheumatism The responsible organism is thought to be a hæmolytic streptococcus group A but while there is an increase in streptococcal antibodies [especially antistreptolysin O (ASO)] in rheumatic children these organisms are very rarely found in affected hearts or joint fluids Accordingly the theory has been advanced that acute rheumatism is one of several post streptococcal states and is dependent upon an abnormal antigen antibody response That hypersensitivity does play a role is supported by the experiments of Rich and Gregory (1943) and others who have induced serum sickness in animals and produced very similar visceral lesions to those found in acute rheumatism Another ætiological factor that should be mentioned is that Wilson (1943) believes that acute rheumatism is a hereditary disease and carried as a single autosomal recessive gene

There is therefore now a large superstructure built on a few distinct foundation stones that acute rheumatism is a disease resulting from *an abnormal response to infection by hæmolytic streptococci group A* and the abnormal response is in some way a hereditary characteristic

Clinical The common features of acute rheumatism are migrating polyarthritis involving especially the knees and ankles fever carditis subcutaneous nodules erythema marginatum and tachycardia or bradycardia There is no specific test for the disease but the erythrocyte sedimentation rate is usually increased Carditis may be manifested by heart failure pericarditis with or without effusion and various murmurs Systolic murmurs are very common and if loud and persistent and associated with cardiac enlargement usually indicate permanent cardiac damage Transient apical diastolic murmurs (Carey Coombs murmur) may not indicate permanent damage but should be regarded seriously Bradycardia occurs in about one third of patients *(Glazebrook and Thomson 1941) Nodules are more*

common in children and practically always indicate carditis the carditis is probably active when further crops of nodules are occurring but is not necessarily active in the presence of persisting nodules The less common rheumatic manifestations are abdominal pain (rheumatic pseudo appendicitis) rheumatic pneumonitis with migrating pul monary infiltrations due to hæmorrhagic alveolitis epistaxis and mental disturbance thought to be due to a cerebral arteritis

Electrocardiographic evidence of prolongation of the PR interval is probably of little diagnostic importance (Reyersbach and Kuttner 1940) but it is interesting that the time honoured sign of grave rheuma tism a soft first heart sound is associated with delayed auricular ventricular conduction (Levine 1948) Prolongation of the Q T interval is also of little value being merely part of the overall estimate of activity (Craige *et al* 1950)

Treatment Salicylates retain an important place in the treatment of acute rheumatism They do not however appear to have any in fluence in preventing chronic carditis even when given in massive doses as advocated by Coburn (1944) Their mode of action has recently been investigated by Reid *et al* (1950) who found that the principal pharma cological actions are to stimulate protein katabolism and aggravate a respiratory alkalosis As a result of increased protein breakdown there is a reduction in cellular water later followed by a decrease in plasma volume and this dehydrating action is associated with relief of joint pain and swelling and a fall in the erythrocyte sedimentation rate

In 1949 Hench announced that Compound E (Cortisone) had a favourable effect on three patients suffering from acute rheumatic fever and carditis and it was assumed that pituitary adrenotrophic hormone (ACTH) would probably have the same effect A year later Massell and his colleagues in Boston published a report on ten patients treated with ACTH for periods of 10 days to 14 weeks In general the clinical response was satisfactory in nine patients and in three significant systolic and diastolic murmurs regressed The fluid retaining proper ties of ACTH were generally controlled by a low sodium diet and mercurial diuretics

The mode of action of these drugs is unknown but Hench (1950) has developed the hypothesis that a susceptible rheumatic subject is sensitised by inherited or environmental factors and develops what might be called the latent rheumatic state When an unknown irritant probably produced by hæmolytic streptococci in the throat is present in a patient in a latent rheumatic state a clinical attack of rheumatic fever will develop The reaction is in two parts exudative and proliferative and there is evidence that cortisone or ACTH can suppress both reactions These hormones do not shorten the duration

of the latent rheumatic state which is probably between 6 and 12 weeks, and if withdrawn prematurely relapse will follow The ultimate possibilities of these and related drugs are great but they are not yet the panacea for acute rheumatism

Prevention On the basis that throat infections with hæmolytic streptococci are intimately associated with clinical attacks of rheumatic fever attempts have been made either to treat such infections at the earliest possible moment or to prevent them altogether It is doubtful whether it is possible to provide treatment sufficiently early to prevent rheumatic fever but there is considerable evidence that hæmolytic streptococcal infections and subsequent rheumatic fever can be prevented For this latter purpose penicillin is superior to sulphonamides because it is less toxic and less likely to produce resistant strains of bacteria *Oral* penicillin is obviously convenient to use but it must be realised that about four fifths of its activity is destroyed in the gastro intestinal tract Penicillin or other newer antibiotics however, *do offer great hope in preventing rheumatic fever if given daily* during at least the winter months to rheumatic subjects

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PULMONARY HYPERTENSION

In normal man at rest the systolic pressure in the pulmonary artery ranges from 20 to 30 mm Hg and the diastolic from 7 to 15 mm Hg The vascular resistance is so low and the distensibility so great that on exercise the blood flow through the lungs must become more than three times the normal before pulmonary hypertension develops (Riley *et al*

1948) In conditions such as atrial septal defect the pulmonary blood flow may reach as much as 15 litres per minute before pulmonary blood pressure rises (Healey *et al* 1950)

In what pathological circumstances then does the pulmonary blood pressure rise? It may do so in the following states —

(1) Left ventricular failure
(2) Diseases of the mitral valve
(3) Following massive pulmonary embolism
(4) In association with chronic pulmonary disease
(5) When there is alteration in the structure of the pulmonary arterioles as in primary pulmonary hypertension
(6) In various forms of congenital heart disease

Suffice it here to say that the hypertension in the first two categories is at least partially reversible by appropriate therapy with digitalis and aminophylline In mitral stenosis despite pathological changes in the arterioles and sometimes in the capillaries successful valvulotomy has been found materially to reduce pulmonary hypertension

In pulmonary embolism it is probable that about two thirds of the arterial tree has to be obstructed before the signs of acute cor pulmonale develop Certainly this is true in anæsthetised dogs (Daley *et al* 1951) and in man without other serious disease Death from pulmonary embolism does not occur unless there is either a large embolus lying in the vicinity of the pulmonary artery bifurcation or there have been repeated smaller pulmonary emboli Death appears to result from mechanical obstruction rather than from generalised pulmonary vasoconstriction following the lodgement of a small embolus The treatment of acute pulmonary embolism is unsatisfactory and the best that can be done is to nurse the patient flat in an oxygen tent and give such drugs as aminophylline (0 48 gramme) or coramine (10 ccs) intravenously Anticoagulants should of course be given to prevent recurrence and to diminish retrograde thrombosis in the pulmonary arteries

Pulmonary hypertension in association with chronic lung disease is always secondary to emphysema It is frequently aggravated by respiratory infection and bronchial spasm whether the emphysema be the result of pneumoconiosis congenital cystic lung kyphoscoliosis recurrent bronchitis or asthma

It is unlikely that the restricted vascular bed of emphysema causes much pulmonary hypertension at rest but on effort such an abnormal vasculature is often unable to accommodate an increased blood flow Important as this factor is the main disability of emphysema is the large lung residual air volume and consequent anoxia Anoxia not only causes an increased blood volume polycythæmia and an increased cardiac output but it also has an action in increasing the tone of the

pulmonary vessels (Motley *et al* 1947) Thus the right ventricle has to maintain a raised stroke volume and works against a higher pressure Any increase in anoxia, usually due to a *respiratory infection may lead* to cardiac failure Cardiac failure in these circumstances is treated by antibiotics and antispasmodics Oxygen therapy should always be used but care must be taken not to produce carbon dioxide intoxication as these patients even when not in cardiac failure have high blood carbon dioxide tensions, this can to some extent be guarded against if oxygen is not given continuously To control restlessness which is so common pethidine and paraldehyde are moderately effective, whereas morphia, with its respiratory depressant action may cause death Digitalis is indicated when the cardiac output has fallen and the extremities are cold and is sometimes of benefit even if the output is moderately raised If œdema is severe and the venous pressure much raised mercurial diuretics and a low sodium diet should be used When every effort has been made to lessen bronchial infection and reduce anoxia and yet a state of chronic failure and lowered arterial oxygen saturation remains it is sometimes worth while endeavouring to lower the basal metabolic rate with thiouracil

In so called primary pulmonary hypertension there are usually irreversible structural alterations in the calibre of the smaller pulmonary arteries and arterioles The ætiology of these changes remains obscure Rarely however a similar clinical picture can result from repeated small pulmonary emboli In either circumstance there is *mechanical blockage to the circulation* and while anoxia may precipitate right ventricular failure the cardiac output is always reduced and therapy of no avail

In Eisenmenger s complex there is also a structural reduction in the size of the pulmonary vascular bed which may be regarded as an adaptive mechanism to raise pulmonary blood pressure and reduce excessive intracardiac shunting of blood Pulmonary hypertension also rarely occurs in auricular and ventricular septal defects and in a few cases of patent ductus arteriosus

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PHEOCHROMOCYTOMA

Pheochromocytomata are chromaffin tumours of the adrenal medulla They cause a variety of symptoms the majority of which are hyper tensive in nature ✓Very rarely they may compress the adrenal cortex and produce an Addisonian state Although they are not common being found in only 0 47 per cent of 1 700 patients subjected to lumbo dorsal sympathectomy (Smithwick and Graham 1951) their impor tance lies in their differentiation from other causes of hypertension Fortunately only a minority are malignant

The clinical diagnosis of these tumours is comparatively easy when they cause paroxysmal attacks of hypertension Such attacks are characterised by the sudden onset of pallor palpitations sweating nausea or vomiting headache and pains in the extremities and lumbar region Sometimes there is also angina pectoris transient glycosuria and even cardiac failure with pulmonary oedema During attacks the blood pressure is greatly raised Between attacks there are usually no symptoms and the blood pressure may be normal (MacKeith 1944) Unfortunately such attacks are comparatively rare and while they may ultimately be replaced by permanent hypertension a number of patients first present with the symptoms of essential hypertension In the latter group the diagnosis may occasionally be suggested if headache is out of proportion to the blood pressure level and is accom panied by sweating sinking sensations and mental turmoil (Cole 1950)

There is considerable discussion as to the proportions of adrenalin and noradrenalin secreted by these tumours but judging from the lack of similarity between the symptoms of patients suffering from pheo chromocytoma and the symptoms of patients undergoing adrenalin infusions it is probable that noradrenalin is the main agent secreted It is also known that noradrenalin increases peripheral vascular resistance

There is no one confirmatory test for pheochromocytoma but the following tests may be very helpful —

(1) Pressure in the loins by bending or massage may rarely induce a hypertensive paroxysm
(2) The B.M R is raised but it is also of course in many other conditions
(3) Glucose tolerance curves may be diabetic in type

(4) Intravenous injection of adrenolytic benzodioxanes 933F (*Fourneau and Bouet 1933 Goldenberg et al 1947*) are said to 'block' the adrenalin like substances produced by pheochromocytoma and consequently lower blood pressure but to have no effect on other forms of hypertension It is obvious that such drugs must be given in a hypertensive phase and indeed they may themselves cause hypertension if given to normal individuals The method of administration is to give an intravenous saline drip for sufficient time to observe a constant blood pressure level 933F, in the dose of 0 25 mg per kg of body weight is then given through the drip over a period of two minutes The blood pressure is recorded during and after the injection for several minutes The results have not always been reliable and untoward symptoms have occurred but the test is used by many and help has been derived from it

(5) Intravenous injection of histamine (0 025 milligram) (Roth and Kvale 1945) raised the blood pressure of patients with pheochromocytoma but not the blood pressure of other patients If a tumour is present very unpleasant symptoms may result and the tests should be used in the order listed here

(6) Very recently Engle and von Euler (1950) have described a method of assaying noradrenalin in the urine and this should ultimately become a most useful diagnostic test

(7) To locate the site of a tumour which is usually impalpable a little help may be forthcoming from intravenous pyelography but generally confirmation is required by laparotomy Perirenal insufflation of air and subsequent X rays are not reliable and at times dangerous

If there is sufficient evidence to recommend operation care should be taken not excessively to handle the tumour and infusions of benzodioxanes and noradrenalin should be available to combat excessive rise or lowering of blood pressure The operative mortality is high but if removal is successful blood pressure should return to normal

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THE COLLAGEN DISEASES

This embracing title is used to cover all conditions associated with alteration in collagen Of necessity it includes alteration in the collagen content of the walls of blood vessels and hence such diseases are legitimately described in this chapter The alternative title of *visceral arteritis* is probably too restrictive and implies that the basic lesion is vascular a view held by some Diseases which may be grouped under this heading are rheumatic fever polyarteritis nodosa disseminated lupus erythematosus dermatomyositis scleroderma and rheumatoid arthritis The list is constantly being extended and sometimes for convenience of classification rather than the dictates of accuracy

It is believed that such diseases represent non specific manifestations of anaphylactic hypersensitivity to various antigens In some way the response to hypersensitivity is related to the pituitary adrenal axis and The General Adaptation Syndrome of Selye discussed elsewhere in this book Despite the immediate lack of clarity between hormonal and hypersensitivity mechanisms the concept has been of considerable therapeutic advantage and all these conditions respond to a varying extent to A C T H and cortisone

Here it is proposed only to discuss polyarteritis nodosa disseminated lupus erythematosus dermatomyositis and scleroderma

Polyarteritis Nodosa

Polyarteritis nodosa was first defined by Kussmaul and Maier in 1866 since when over 400 cases have been recorded The frequent finding of co incidental streptococcal and other infections at first led to the conclusion that it was infective in origin Subsequently the occurrence of lesions in patients dying after serum sickness or after the development of hypersensitivity to sulphonamides and the experimental production of the disease sometimes accompanied by glomerulonephritis in rabbits after the establishment of an anaphylactic state (Rich 1942) by repeated injections of foreign serum (Rich and Gregory 1943) indicated that some cases at least resulted from hypersensitivity to various antigens It seems likely that the responsible antigen is usually bacterial but organic arsenicals thiourea desoxycorticosterone acetate and iodine have all been incriminated as possible ætiological agents and it is interesting that 1ͺ per cent of cases have a past or family history of allergic phenomena (Harris Lynch and O Hare 1939) Selye (1946) has also reproduced the disease in animals by overdosage with anterior pituitary lobe or cortical hormones

The vascular lesions may be limited to one organ or may be scattered throughout the vascular tree evoking a symptomatology so varied that until recently the diagnosis was rarely made in life There are however, a number of features which should enable a correct diagnosis to be made in a large proportion of cases It is a disease of all ages more common in males with an average duration of 6 to 12 months and recovery in at least 50 per cent There is an acute febrile onset in more than half the cases recorded and the remainder are usually febrile at some time in their course, and have tachycardia out of proportion to the fever Polymorphonuclear leucocytosis occurs in the majority, and is accompanied by an elevated E S R Leucopenia with relative lymphocytosis is rare, and eosinophilia so often regarded as a diagnostic feature occurs in less than 20 per cent and then usually in association with asthma Moderate anæmia of normochromic or hypochromic type is usual The kidneys are almost always involved and sometimes glomerulo nephritis is superadded Albuminuria and microscopic hæmaturia are common and a noteworthy finding is the occurrence of casts of all types in a single urine specimen unlike the cylinduria of true nephritis (Krupp 1943) Massive hæmaturia is the result of vessel rupture or large renal infarcts Hypertension occurs even in the absence of glomerulo nephritis and often with widely variable systolic readings Œdema may be of cardiac or renal origin or may accompany polymyositis and may mask wasting which is almost invariable

Involvement of individual systems and organs gives rise to more specific signs Subcutaneous nodules are rare but represent the actual arterial lesions and are sometimes accompanied by erythematous urticarial or purpuric eruptions Biopsy of nodules when these are present is the surest way of confirming the diagnosis isolated muscle biopsies being much less reliable Rupture of visceral nodules may lead to cerebral alimentary or retro peritoneal hæmorrhage and arterial occlusion to myocardial hepatic renal pulmonary pancreatic or splenic infarcts Obliterative arteritis of the vasa nervorum is responsible for painful usually asymmetrical peripheral neuritis and lesions of the cerebral vessels may cause convulsions cranial nerve palsies hemiplegia and pupillary inequality The fundal changes are sometimes diagnostic with multiple retinal detachments unevenness of the calibre of retinal vessels and miliary perivascular patches of pale choroidal exudate but in the later stages hypertensive retinitis often masks the picture

Pathologically there is a necrotising panarteritis of small elastic arteries with fibrinoid necrosis affecting all coats but initially the inner media and subintima with periarteritis as a secondary phenomenon At first there is infiltration with polymorphonuclear cells later replaced

by eosinophils in the thrombosed lumen and scarred walls Healing by granulation may be complete but the weakened wall may yield forming multiple small aneurysms The lesions occur in crops along the length of the vessel and may involve only a segment of the circumference one of the most remarkable features being the occasional tendency to involve only one organ or system with the result that no single clinical finding is invariably present

There have been some reports of improvement following treatment with sulphonamides or penicillin and it has been assumed that in these instances the responsible antigen was bacterial Recently a few patients have been treated with A C T H with dramatic result and it is of great interest that Morgan Rich and Griffith (1950) have found a reduction in cardiovascular lesions following A C T H administration to animals with induced anaphylactic hypersensitivity

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Disseminated Lupus Erythematosus

The skin manifestations of this disease long recognised by dermatologists and separated from other forms of lupus have only in recent years been regarded in their true perspective as part of a generalised disease The frequent association of antecedent streptococcal tuberculous and other infections and the report of its development following the injection of antitetanus serum (Fox 1943) all suggest an allergic basis Also the marked hypersensitivity to Rh and other red cell

antigens is a point of practical interest The occasional sensitivity to sunlight is probably not an important ætiological factor in the disseminated form of the disease The erythematous macular rash with its characteristic facial ' butterfly " distribution and tendency to spread to the front of the chest finger tips palms, soles, pressure points and mucous membranes, and frequent telangiectatic and purpuric elements may precede accompany or succeed the visceral phenomena and in some cases may even be absent altogether

The disease is commonest in the second to fourth decades and is extremely rare in males The onset is sometimes abrupt with the simultaneous advent of skin and generalised signs terminating rapidly with high fever prostration and delirium in over 90 per cent of cases More commonly the onset is gradual the course prolonged and remittent with death supervening in about 50 per cent in months or years but complete recovery occurring in a few In the latter group low grade irregular fever and painful polyarthritis are usually the presenting signs and not infrequently lead to a diagnosis of rheumatic fever or rheumatoid arthritis but as the disease progresses there may be involvement of other serous membranes leading to pericarditis pleural effusion and abdominal pain There is usually a moderate leucopenia hypochromic anæmia and thrombocytopenia and serological tests for syphilis are sometimes falsely positive Adenopathy has often been described but splenomegaly is rare Involvement of the renal vessels gives rise to albuminuria microscopic hæmaturia and cylinduria of all types and terminally there may be œdema of the extremities and eyelids Retinoscopy demonstrates direct evidence of vascular damage with perivascular hæmorrhages arterial segmentation and scattered fluffy exudates but curiously the blood pressure is seldom elevated Recently examination of bone marrow of patients suffering from active disseminated lupus erythematosus has shown two peculiarities polymorphonuclear leucocytes containing small inclusions (tart cells') and clumping of leucocytes (Hargraves Richmond and Morton 1948) These two peculiarities are known together as the *L E phenomenon* Haserick (1950) has further examined the phenomenon and has detected a factor in plasma related to gamma globulin which when added to normal marrow produces clumping of leucocytes and ultimately *L.E cells* with inclusions This factor is stable for long periods when sterile and is inhibited by antibodies developed in rabbits against the gamma globulin of the plasma of patients suffering from acute disseminated lupus erythematosus It is absent in phases of remissions and in allied conditions and offers considerable hope of being a valuable diagnostic aid

Fibroid degeneration of collagen is the basic lesion in disseminated lupus erythematosus being found not only in vessel wall and skin

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but also in many other situations There is autopsy evidence of wide spread damage to arterioles and capillaries The endothelium is thickened with thrombus formation or there are degenerative or necrotising changes in the walls with hæmorrhages into adjacent tissues Any organ may be involved but the renal glomeruli almost always show some degree of change with wire loop capillaries and necrosis of the tuft In about 30 per cent of cases the cardiac valvular endothelium is covered by small verrucose or broad flat vegetations which in life may be responsible for harsh systolic murmurs These lesions were first described by Libman and Sacks (1924) and regarded as distinct from rheumatic valvulitis in their different macroscopic appearance and absence of typical Aschoff nodes Since then they have been recorded both in disseminated lupus erythematosus and polyarteritis nodosa

Treatment in the past has been by a variety of agents ranging from vitamin E calciferol and antibiotics to the heavy metals The limited experience yet available suggests that A C T H and cortisone exert a beneficial if temporary effect

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Dermatomyositis

Dermatomyositis as its name implies is primarily a disease of skin and muscle but as in the other conditions of this group many other organs may be involved and this is especially true of the heart blood vessels fat and intestines (Wainger and Lever 1949) It occurs at all ages but is commonest between the ages of 20 and 40 The course may be acute ending in death within a few weeks or chronic and relapsing for months or years

A common onset is with fever weakness muscle aching and tenderness œdema of the face and eyelids and erythema of the face neck chest and extremities which is dusky or resembles toxic erythema or urticaria Either œdema muscle weakness or skin changes may be the prominent symptom As the œdema subsides the skin becomes rough and changes in pigmentation and telangiectases sometimes appear Muscle weakness is often most obvious when a patient is

asked to rise from touching his toes Later the muscles become hard wasted and retracted Creatinuria is a constant feature and dysphagia splenomegaly adenopathy and eosinophilia sometimes occur The electrocardiogram is often of low voltage with generalised T wave inversion

Klemperer, Pollock and Boehr (1941) established the basic morphological change as degeneration of collagen which is almost certainly of the same nature as in diffuse scleroderma but is accompanied in the muscles in dermatomyositis by a pronounced inflammatory reaction Probably the primary disease is not vascular but the vessel walls contain collagen and are therefore involved Fibrosis appears to be the sequel of degeneration

Treatment consists of bed rest until improvement occurs A C T H and cortisone have not yet had an extensive trial but their effect does not appear to be as marked as in allied conditions If treatment can tide over an acute phase until a spontaneous remission occurs such drugs however, may still be of considerable value

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Scleroderma

Scleroderma is a disease of middle life and is more common in females than males Of the several forms of the disease the two most frequently encountered are *sclerodactyly* which follows Raynaud s phenomenon and especially involves the hands forearms face neck and scalp and *the amorphous form* The latter usually begins insidiously with stiffness numbness and brawny œdema Months or years later the cutaneous tissue becomes indurated and atrophy and ulceration follow Atrophy may occur in small punctate areas (morphœa) or be more generalised with dry white or pigmented skin and loss of hair Facial atrophy produces a mask like expression the fingers become tapered and the nails curved and irregular The process may involve the lungs the œsophagus the large intestine the heart the thyroid gland the central nervous system skeletal muscle and the kidneys The bones may become rarified and the peridontal space increased in width Disturbance of calcium metabolism presumed to

be due to parathyroid dysfunction may result in the subcutaneous deposition of calcium Histologically there is an increase in pre existing bundles of connective tissue medial arterial proliferation and roundcell infiltration of the adventitia In the viscera there is œdema cellular infiltration increase in connective tissue and ultimately atrophy of the parenchyma

The disease is often punctuated by remissions and exacerbations before secondary infection leads to death More rarely dysphagia becomes intense or heart failure supervenes A C T H cortisone and even testosterone (Hertz and Forsham 1950) may all induce transient remission but it is not yet known whether they can alter the fundamental course of the disease

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ELECTROCARDIOGRAPHY

The last fifteen years have seen great advances in the knowledge of electrocardiography The credit for this is largely due to the work of F N Wilson and his associates at Ann Arbor University Wilson brought to the subject a brilliant mathematical mind and in F D Johnston he had a colleague with a great understanding of electricity Experimental work with dogs and the use of præcordial leads in clinical practice enabled them to confirm and expand the original discovery of Wolferth and Wood (1932 1933) that information could be gained by the use of præcordial leads which could not be provided by the standard leads alone The other main advances have come from the use of the so called unipolar leads These are the Voltage or V leads of Wilson (1934) and the Augmented Voltage or aV leads of Goldberger (1942) These new methods have not only made electrocardiography more accurate but also have made electrocardiograms (E C G s) easier to interpret

Theoretical Considerations All living muscle cells produce minute electrical currents during contraction Craib (1930) showed that by applying electrodes (the exploring electrodes) to an isolated

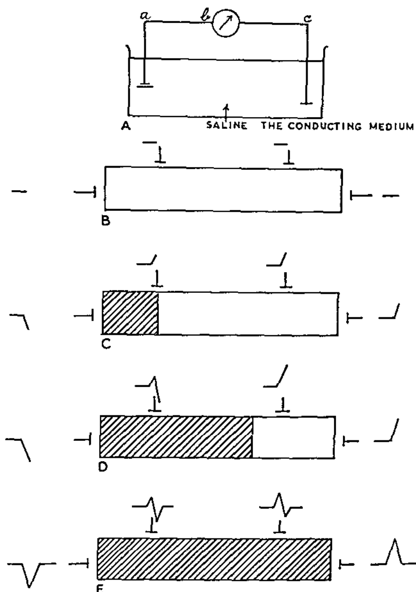


FIG 11 Electrical effects produced in the process of contraction by an isolated muscle strip in a bath of saline A the saline bath The isolated muscle strip is represented by the line beneath the exploring electrode a b the galvanometer c the indifferent electrode (The exploring electrode is insulated from the surrounding saline and makes electrical contact only with the muscle strip) B isolated muscle strip enlarged Electrical activity has not begun The four exploring electrodes record no potential and the galvanometers trace the iso electric line C D and F the depolarisation process passes from the left to the right end of the strip (cross hatched) Electrodes facing the advancing wave record a positive potential Those facing the back of the wave a negative potential (*Modified from Hill* (19.0))

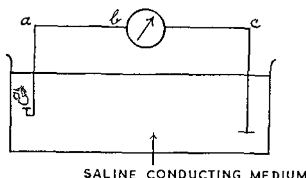
muscle strip in a conducting medium and connecting the electrodes through a suitable galvanometer to a distant electrode (the indifferent electrode) in the same medium the changes of electrical potential occurring in the muscle during contraction could be recorded The galvanometer most generally used is a modification of the Einthoven quartz fibre galvanometer The current is led through the silver coating of a quartz fibre of about the diameter of an erythrocyte suspended between the poles of an electromagnet When the current flows the fibre moves in the magnetic field and the movement of the fibre is recorded by an optical system which throws its shadow through a slit on to a moving photographic plate It is so arranged that when the exploring electrode is positive relative to the indifferent electrode the movement of the fibre is registered as upward on the plate Many modern electrocardiographic machines have other forms of galvanometer (mirror galvanometer direct writing styluses etc) but they are all contrived to give records comparable to those of the quartz fibre galvanometer

It will be seen from Fig 11 that as the wave of excitation passes along the muscle strip electrodes facing the advancing wave record a positive deflection and those facing the back of the wave record a negative deflection As the wave passes beneath an electrode the potential changes from positive to negative To this process in the muscle the name depolarisation is given It is suggested by Hodgkin and Huxley (1945) that changes in the permeability of the cell to sodium and potassium ions may be responsible for the electrical effect After depolarisation the muscle returns to the resting phase a process called repolarisation and in doing so produces changes of potential which can also be recorded (This is not included in Fig 11)

From the apex of the exposed heart of a frog similarly mounted in a conducting medium an exploring electrode coupled through a galvanometer to an indifferent electrode distant in the medium records changes of potential as shown in Fig 12 The first positive deflection or P wave results from the depolarisation process in the auricle and the second upward deflection or R wave from the depolarisation of the ventricle The third upward deflection the T wave is due to repolarisation of the ventricle (In the human the repolarisation of the auricle or auricular T wave is rarely seen but when it is its direction is usually opposite to that of the P wave Generally it is lost in the larger potential changes produced by ventricular depolarisation)

It is not difficult to imagine that in the isolated muscle strip the longer the strip the longer an electrode facing the wave of excitation would register positivity and consequently the larger would be the area under the R wave recorded by such an electrode This is in fact

the case Similarly the thicker the heart muscle the larger the area under the R wave



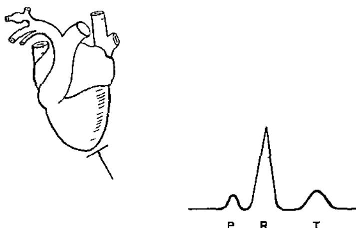


FIG 12 Electrical effects recorded from the apex of the isolated frog s heart Notation as in Fig 11 The galvanometer records a P wave produced by auricular depolarisation followed by an R wave of ventricular depolarisation and a T wave of ventricular repolarisation

So far only the changes of potential occurring at the exploring electrodes have been considered The distant electrode through which the circuit is completed because it is distant records very much smaller changes of electrical potential These systems may be called in the case of the isolated muscle strip unipolar ' electromyograms and in the case of the isolated heart unipolar electrocardiograms From the theoretical aspect such systems are much easier to understand than bipolar electrocardiograms recorded from two points on the muscle strip The fact that until latterly all electrocardiograms were bipolar delayed a fuller understanding of them

If an intact animal is immersed and an electrode applied to the skin over the apex of the heart (and insulated except at the point of contact) a galvanometer interposed between this and an indifferent electrode in the conducting medium will record tracings similar to those from the isolated heart In clinical practice subtotal immersion of the patient is not a practicable procedure If however one terminal of the galvanometer is connected to the exploring electrode and the other to multiple electrodes on the

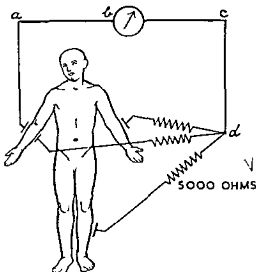


FIG 13 Recording VR by the Wilson method Notation as in Fig 11 d, the central terminal (As in the previous diagrams the electrodes are in direct contact with the underlying tissue although drawn as separate.)

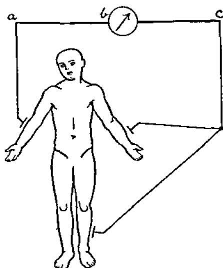
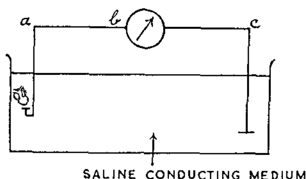


FIG 14 Recording aVR by the Goldberger method (There is some evidence that this technique is improved by introducing resistances similar to those used in the Wilson method between the plates of the indifferent electrodes and the junction of their lead)

surface of the body an electrocardiogram similar to the unipolar electrocardiogram results In Wilson's method the indifferent electrode or so called central terminal is obtained by joining leads from three limbs (Fig 13) each through a 5 000 ohm resistance to one terminal of the galvanometer The exploring electrode is connected to the other terminal This the Voltage or V lead is not strictly a unipolar lead because changes of potential undoubtedly do occur at the central terminal It is Wilson's (1947) claim that the changes are not

the case Similarly the thicker the heart muscle, the larger the area under the R wave



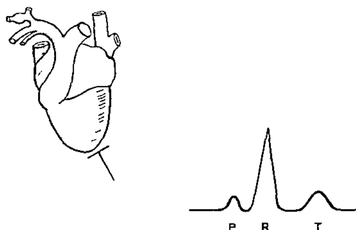


FIG 12 Electrical effects recorded from the apex of the isolated frog s heart Notation as in Fig 11 The galvanometer records a P wave produced by auricular depolarisation followed by an R wave of ventricular depolarisation and a T wave of ventricular repolarisation

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are then depolarised from within outwards and the subsequent form of the QRS complex will depend on the relative bulk of the two ventricles and the rate of depolarisation in each. Normally as the *left ventricle is thicker than the right, its depolarisation produces* a greater potential than the right and an electrode over it records a tall R wave. An electrode over the right ventricle records the positive

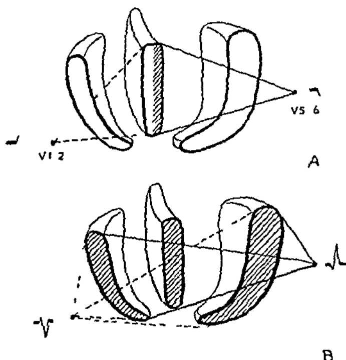


FIG. 15. Ventricular depolarisation as recorded by unipolar electrodes in the V1 or V2 and the V5 or V6 positions. The depolarisation of the septum is recorded as a primary R wave at V1 and as a Q at V5. (*After Oram* (1940).)

effect due to the depolarisation wave of the right ventricle advancing towards it but also the negative effect due to "seeing" the back of *the depolarisation wave in the left ventricle*. The latter being of greater potential is responsible for the S wave being larger than the R wave recorded from leads over the right ventricle. Each præcordial electrode registers the sum of the changes of potential occurring in its field of "vision". As depolarisation advances towards the proximal epicardium a positive deflection is recorded until the advance reaches the epicardium when the electrode becomes negative. The point when the underlying epicardium is depolarised is variously placed on the

more than 0 3 mv Katz (1950) summarises the position well when he says "Thus the Wilson central terminal is not a null electrode but one that approaches this state better and more consistently than any other distant electrodes routinely employed" The changes at the central terminal are negligible when the exploring electrode is near the heart, but may make as much as 20 per cent difference when the exploring electrode is distant from the heart for example when recording the "unipolar" limb leads—VR VL, and VF

Goldberger (1942) showed that if the exploring electrode was connected to one limb and the "indifferent" electrode to two others (Fig 14) the potential differences recorded were similar in form to but 1 5 times as great as, those recorded by Wilson s method He called these the Augmented Voltage, or aV leads [Cronvich *et al* (1950) have shown that if the electrodes do not make equally good contact with the skin the indifferent terminal resembles more nearly the electrode with the less resistance, so that the tracing approaches a bipolar one] Although the aV limb leads and to a less extent the V limb leads are open to more theoretical and practical objections than the V praecordial leads, they have been found to be of value in clinical practice

Before the practical applications of these new leads can be understood it is essential to master a few further theoretical considerations In the experimental animal, if the exploring electrode of a unipolar circuit is placed in the cavity of a ventricle, the changes of potential recorded are equal in force and opposite in sign, to those recorded from the apex of the heart (Johnston *et al* 1935, Wilson *et al*, 1934) By introducing the exploring electrode on the tip of a cardiac catheter into the right ventricle in the human potential changes similar to those found in the experimental animal are recorded (Sodi Pallares *et al* 1947) An electrode facing the cavity of the ventricles though at a distance from the heart records a similar tracing Normally the exploring electrode in VR or aVR is in such a position and records an inverted P wave a deep S wave and an inverted T wave The analogy of the electrode being an 'eye' in this case seeing 'the cavity of the ventricle is useful The cavity and apex electrodes are strictly comparable to the electrodes at opposite ends of the isolated muscle strip (Fig 11)

Fig 15 is a diagram of the depolarisation process passing through the heart It will be clear from examination of this that the septum is the first part of the ventricle to be depolarised and the wave passes from the left side of the septum to the right. An electrode over the right ventricle will therefore face the advancing wave and an R wave result conversely an electrode over the left ventricle will see 'the back of the wave and register it as a Q wave The

found or by a persistent T wave inversion or by a combination of the two Wilson (1947) stresses that the Q wave is much the more reliable sign because T wave inversion can result from many causes of which the commonest is digitalis therapy

In this section the author has drawn freely from the review of Wilson (1947) and the monographs of Oram (1949) and Hill (1950) To these the reader is referred for a more complete analysis

Technique in Clinical Electrocardiography

Technically inadequate electrocardiograms are so prevalent and the misinterpretation of them which may result potentially so dangerous that a consideration of a few technical points may not be out of place

The electrodes must make as good a contact as possible this demands adequate amounts of good electrode jelly well rubbed in but not allowed to spread from one chest electrode site to another The patient should be warm and relaxed a little explanation and reassurance will often remove somatic tremor and abolish a tachycardia The patient conveniently from a plate on the right leg and the machine should be earthed

The position of the chest leads have been arbitrarily established (American Heart Association 1943) Position 1 is in the fourth inter costal space at the right edge of the sternum 2 is in the fourth inter costal space at the left edge of the sternum 4 in the left mid clavicular line in the fifth inter costal space and 3 mid way between 2 and 4 Five 6 and 7 are in the anterior mid and posterior axillary lines in the same transverse plane as 4 Their relationship to the normal heart is ap proximately shown in Fig 17 If the indifferent elec trode is the central term inal of Wilson the leads are called CV1 CV2 etc or for brevity V1 V2 etc If the indifferent electrode is on the right arm the leads are called CR1 CR2 etc Except where there is a special indication it is usual for three chest leads only to be recorded often V1 V3 and V6

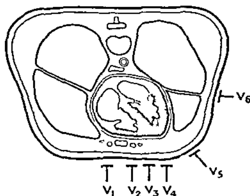


Fig 17 The position of the chest electrodes with reference to the heart The ventricular wall is stippled (*Hill* 1950)

negative deflection following the R wave, and was called by Lewis and Rothschild (1915) the point of intrinsic deflection [Sodi Pallares *et al* (1950) have shown the moment when the process reaches the epicardium underlying a unipolar chest electrode to be at the nadir or on the lower third, of the S wave] It cannot be too strongly stressed that a chest electrode records not only what is occurring directly underneath it, but the sum of the electrical effects in the cone of its "vision"

It has long been known that when *heart muscle is injured* changes in the pattern of electrical activity occur The theoretical explanations of this are still not generally accepted The experimentally proven fact however remains that an exploring electrode which has such an injured area beneath it shows an upward shift of the ST segment (Fig 16) There is some evidence that this may be partly spurious, due to a downward shift of the T P segment (Bayley *et al* 1944) Herein lies one of the great simplifications of unipolar electrocardiography that the pattern produced by injured myocardium is usually fairly typical, and one has only to find in which unipolar leads there is an upward shift of the ST segment to know that in that lead the exploring electrode is facing the injured area Conversely an electrode facing the endocardial surface of an infarcted area records a downward shift of the ST segment If the injury is such that death of heart muscle results the dead area no longer has any electrical activity It then acts as a window through which the changes of potential occurring in the cavity are conveyed to an overlying exploring electrode and a QS or QR pattern of the intracardiac electrode is recorded [It has already been shown that depolarisation of the septum can produce a Q wave when the exploring electrode faces the left ventricle For a Q wave to be regarded as evidence of infarction it must be at least one quarter the height of the subsequent R wave (Wilson *et al* 1947)] By a similar process the T wave can become inverted An old myocardial infarction may be demonstrated by the presence of a significant Q wave in a lead in which it is not normally

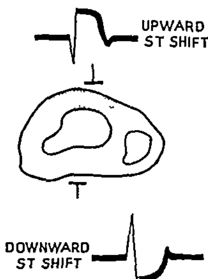


FIG 16 Myocardial infarction The exploring electrode facing the epicardial surface of the infarct records an upward ST shift that facing the endocardial surface a downward ST shift (*After Hill* (1950))

the heart it may only be apparent by examination of VI or aVL the only electrode facing the infarcted area VL or aVL also face some anterior and most antero lateral myocardial infarcts VF or aVF face the base of the heart (Fig 18) and are the most useful leads for localising posterior infarction

Left ventricular hypertrophy may appear in VL or aVL before it appears elsewhere The pattern produced by ventricular enlargement will be discussed more fully in the section on the chest leads The characteristic tall R wave and sagging ST segment can appear in VL or aVI as a result of the heart being horizontal but not hypertrophied (Oram 1949) Rarely the sag of this ST segment can be abolished by making the patient take a deep breath Failure to realise this has resulted in a patient being confined to bed for six weeks with a diagnosis of myocardial infarction TaVL showed an ST sag and T_1 was con sequently of low voltage TaVL became upright on deep inspiration (Evan Jones 1950)

The Use of the V Præ cordial or Chest Leads in Clinical Practice Rotation of the heart about its long *axis may be detected from* an examination of the chest leads The septum usually lies beneath the V3 or V4 electrode (Fig 17) Elec trodes to the right of this have a typical rS pattern and to the left an Rs or qRs pattern If the septum is displaced by clockwise rota tion as seen from below the RS pattern of the septum may be found in V5 or even 6 and if counter clockwise in V2 or V1

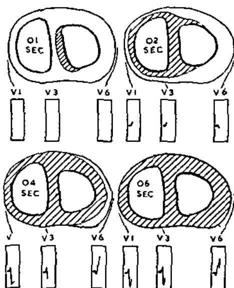


Fig 19 Ventricular depolarisat on as recorded at V1 V3 and V6
A. Normal The depolarisation of the left ventricle produces bigger changes of potent al than the right The R wave is therefore taller at V6 and the S wave deeper at V1

E C C evidence of enlarge ment of either ventricle can be obtained with greater reliability from the chest

Footnote —(Th comb nation of a deep Q and in erted T in the standard leads can be produced without posterio infarction If the heart is horizontal so that the ventri cula complex from the L L (left leg) is almost isoelectric and at the L A (left arm) there is a tall R and T then the mathematical process of subtracting the changes of potential invol ed in lead 3 i e L L L A may produce a deep Q and inverted T in that lead)

Katz (1950) states that an electrocardiogram is 'as good as the judgment of the interpreter' Though this is mainly true it omits the extremely important role of the technician

The Use of V and aV Limb Leads in Clinical Practice The chief use of the V and aV limb leads is in analysing electrocardiograms resulting from different positions of the heart The most obvious of these is that of dextrocardia, where the cavity lead is aVL instead of aVR This is diagnostic of congenital dextrocardia *

Rotation of the heart about an antero posterior axis will also produce changes in the V and aV leads When the heart lies horizontally the ventricular complex of VL or aVL resembles those of V5 and V6 when it lies vertically the ventricular complex of VF or aVF resembles those of V5 and V6 Wilson *et al* (1944) have listed *six cardiographic positions of the heart It is unnecessary to describe* them fully here suffice it to say that three are intermediate between *the horizontal and vert*ical positions already described, and the sixth is indeterminate and no obvious correlation between chest and limb leads can be found Though Wilson (1947) himself lays no claim *that the electrical posi*tion is necessarily the same as the anatomical they are frequently similar This concept of the electrical position of the heart allows the distinction to be made between 'axis deviation in the standard leads due to the position of the heart and that due to hypertrophy of the ventricle

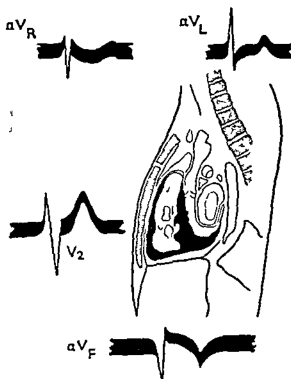


Fig 18 Posterior myocardial infarction The upward ST shift is found in aVF the lead facing the infarcted area (*The ventricular wall is black*) (*Hill* 1950)

If infarction occurs in the high lateral area of the anterior wall of

* In the standard leads lead 1 is inverted and leads 2 and 3 are interchanged It is easy to calculate how this comes about with the knowledge that lead 1 is L.A R.A lead 2 L.L R.A and lead 3 L.L L.A and that in effect the L.A and R.A. leads are interchanged

the heart it may only be apparent by examination of VL or aVL the only electrode facing the infarcted area VL or aVL also face some anterior and most antero lateral myocardial infarcts VF or aVF face the base of the heart (Fig 18) and are the most useful leads for localising posterior infarction

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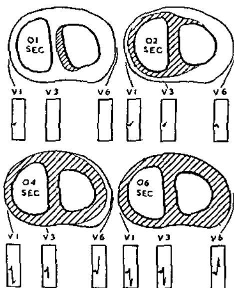
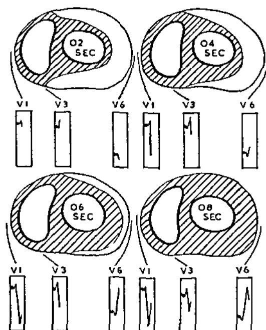


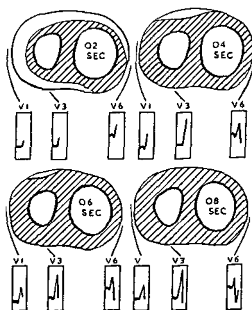
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E C G evidence of enlargement of either ventricle can be obtained with greater reliability from the chest

Footnote —(The combination of a deep Q_3 and inverted T_3 in the standard leads can be produced without posterior infarction If the heart is horizontal so that the ventricular complex from the L L (left leg) is almost isoelectric and at the L.A (left arm) there is a tall R and T then the mathematical process of subtracting the changes of *potential involved in lead 3 i e L L L A.* may produce a deep Q and inverted T in that lead.)



B Left ventricular hypertrophy The RV6 is taller than in the normal and the SV1 deeper The longer time required for the process to pass through the thicker muscle may also result in a widening of the QRS complex If this is more than 0 12 sec it may be labelled left bundle branch block



C Right ventricular hypertrophy RV1 istaller and SV6 deeper than in the normal Frequently an rsR pattern is recorded at V1 (*Modified from Myers* 1950)

leads than from any other method. When the right ventricle is enlarged a tall R wave appears in V1, V2 and often V3. As the enlargement increases a sagging of the ST segment, probably due to overlapping of depolarisation and repolarisation in the thicker muscle, may appear. This is the so called 'ventricular 'strain'' pattern. Many cardiologists believe that these changes are a more reliable indication of right ventricular enlargement than fluoroscopy. Myers (1950) has made an accurate analysis of the præcordial electrocardiograms of right and left ventricular enlargement and it is on his findings that Fig. 19 is based. Left ventricular enlargement produces similar changes in leads facing the left ventricle.

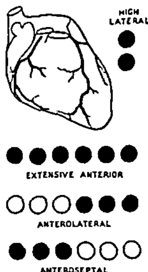


Fig. 20. The electrodes which record the changes of infarction in various types of infarct, e.g. in antero-lateral infarction the changes are found in V4, V5 and V6. (*Hill* 1950.)

Delay in the depolarisation of either ventricle, usually called bundle branch block, is more readily interpreted from chest than from the limb leads. Delay can theoretically occur from two causes: (1) damage to the conducting bundle, or (2) increase in size of the ventricle so that the process has a longer course to follow. Rasmussen and Moe (1948) believe that the latter is the commoner cause of left bundle branch block and suggest that the term 'ventricular delay' should be used. Their conclusions are strongly supported by the frequently observed fact of the progressive widening of the QRS with progressive cardiac enlargement. Similarly with enlargement of the right ventricle (e.g. in Fallot's tetralogy and sometimes mitral stenosis) right ventricular delay may show itself as right bundle branch block. Wilson (1947) demands an rSR pattern in V1 and VE (exploring electrode on the ensiform cartilage) for the diagnosis of incomplete right bundle branch block.*

An antero-septal infarction (Fig. 20) can be frequently localised only from the chest leads. Infarction of the ventricular septum may

* MacGregor (1950) found that direct leads recorded with the exploring electrode on the right ventricle of patients with Fallot's tetralogy at operation showed an rS pattern. He therefore suggests that the rsR pattern so often seen in V1 in patients with enlargement of the right ventricle is due to rotation of the heart in a clockwise direction as seen from below. As a result the tall secondary R wave in V1 may be arising from the left ventricle. Support is lent to this idea by the frequent finding of similar tracings in cases of acute cor pulmonale, for in such cases there is no hypertrophy of the right ventricle, but it may well be that as a result of dilatation of this ventricle there is clockwise rotation of the heart.

manifest itself by the injury pattern in V3 V6 and also in aVF i e the appearances of combined anterior and posterior infarction (Roesler and Dressler, 1947) The epicardial injury produced by *pericarditis* results in an upward shift of the ST segment in all electrodes 'facing' the damaged area if effusion develops the voltage of these leads may become smaller The E C G changes in myxœdema have been attributed partly to pericardial fluid (Schnitzer and Gutmann, 1946)

In the presence of bundle branch block the diagnosis of myocardial infarction presents particular difficulties In 33 patients with clinical evidence of myocardial infarction and left bundle branch block Somerville and Wood (1949) found that 48 per cent showed E C G evidence of infarction In 27 patients with clinical evidence of infarction and right bundle branch block 93 per cent showed E C G evidence of infarction For a further analysis of this problem Dressler *et al* (1950) should be consulted

Finally the chest leads are useful in the interpretation of arrhythmias Auricular activity is often best studied with an exploring electrode in the third space at the right sternal edge

Special Uses of the Electrocardiogram

Electrocardiographic methods of confirming that chest pain is due to myocardial ischæmia include the exercise and anoxæmia tests The latter is considered to be dangerous (Katz 1950) and is not generally used The former is widely used and varies only in detail The principle of the exercise test is to record electrocardiograms at rest and after effort Some use a standard exercise calculated on patient s weight and number of stairs climbed (Master *et al* 1942) while others make the patient exercise to the limit (Wood *et al* 1950) The results depend on which of the methods is used the latter giving a higher proportion of positive results Wood *et al* (1950) using the maximum exercise method found changes in 88 out of 100 patients with a normal E C G at rest and typical angina pectoris The test was positive in only 5 of 12 whose heart rate was not increased by the exercise to more than 90 The typical changes are flat or sagging depression of the ST segment from 1–4 mm below the PQ level V5 is the most frequently positive lead The exercise test is undoubtedly of clinical value

Lengthening of the QT interval is one of the manifestations of acute rheumatism For proper interpretation this must be related to the cycle length (R–R interval) The QTC is $\frac{QT}{\sqrt{R-R}}$ and in health is found to be not more than 0 40s (Taran and Szilagyi 1947)

Potassium deficiency produces electrocardiographic abnormalities These include depressed broadened T waves, prolonged QT interval

depression of the ST segment and prominent U waves following the T waves These are not specific and may occur in other cardiac disturbances In hyperpotassæmia abnormally tall T waves are found (Tarail 1948)

E C G abnormalities have been described in numerous endocrine disorders including thyrotoxicosis myxœdema cretinism Simmond s disease Addison s disease diabetes and hyper and hypoparathyroidism (Evans 1949b) They are also found in Friedreich s ataxia (Manning 1950) and familial cardiomegaly (Evans 1949a) Massive pulmonary embolism is usually associated with E C G abnormalities Wood (1941) found that whenever the venous pressure was elevated as a result of acute cor pulmonale the E C G showed evidence of right ventricular strain Dack and Master (1949) pointed out that in the older age groups the changes resulting from pulmonary embolism may be those of myocardial ischæmia

General Considerations

The diagnosis of myocardial infarction must always be primarily a clinical one (Cassidy 1946) but the electrocardiogram is of great diagnostic aid In a review of myocardial infarction with necropsy control Zinn and Cosby (1950) found that history combined with clinical examination offered evidence of infarction in 70–76 per cent of 256 patients reviewed A single præcordial lead in addition to three standard leads offered patterns suggestive of infarction in 51 5 per cent of the patients Multiple præcordial leads gave evidence of infarction in 80 per cent of 50 patients They conclude that the limitations of three standard leads augmented by only a single præcordial lead are so great that multiple præcordial lead techniques should be a routine procedure whenever the question of myocardial infarction arises

The present shortcomings of electrocardiography as an aid to diagnosis may be overcome largely by an increase in knowledge of those who use it The practice of reporting on the electrocardiogram without adequate knowledge of the clinical details of the patients militates against its effective use Katz (1950) forecasts that the introduction of three plane electrocardiography may be expected to improve the accuracy of the electrocardiogram This method is at present in the experimental stages

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CHAPTER VI

RENAL DISEASES

by

CHRISTOPHER HARDWICK

Tests of renal function Nephritis Acute uraemia Renal infections Renal aspects of hypertension

TESTS OF RENAL FUNCTION

To produce the daily urinary output of 1 5 litres some 7 000 litres of blood flow through the kidneys and about 170 litres of glomerular filtrate are formed (Smith 1937) That such a large volume of blood is required for the production of a relatively small amount of urine suggests that as excretory organs the kidneys are not very efficient These figures however remind us that the chief function of the kidneys is to maintain the biochemistry of the body as constant as possible, the excretion of waste products being incidental to this process They are the chief guardians of the milieu interieure of Claude Bernard, and it is for this reason that about one quarter of the output of the heart goes to them each minute By this means the whole of the circulation is passed through the kidneys very frequently and the slightest adverse change in its composition is quickly corrected

Renal function therefore depends as much upon blood flow as it does upon the efficiency of the nephrons The intricacies of the anatomy of this circulation have recently been exposed by the brilliant work of Trueta and his colleagues (1947) and will be described in a later section The volume of the renal circulation can be estimated by clearance experiments The term clearance was introduced by van Slyke who worked with urea He defined urea clearance as the volume of blood which was cleared of urea in one minute In its passage through the kidney blood is not completely cleared of urine and so the urea clearance is a hypothetical and not a real volume

Nevertheless the test has been widely adopted in clinical medicine and it has been found that in cases of progressive renal disease the down ward course is closely paralleled by decreasing values for the urea clearance

If a substance is excreted by glomerular filtration alone then its clearance will measure filtration rate Homer Smith (1937) has shown that inulin is such a substance it has a clearance of about 120 ml per minute

Similarly if a substance is excreted solely by the tubules then when its concentration is low so that it is completely removed from the blood its clearance will measure the renal blood flow As the concentration of this substance increases there will come a level above which it is not completely cleared by the tubules The clearance at this level represents the maximum tubular activity or tubular excretory mass or Tm (Homer Smith 1937) It must be emphasised that Tm is a measure of function and not of actual tubular tissue Diodone and para amino hippuric acid (P A H) are used for this purpose, in normal adults they have clearances of about 600 ml per minute

Inulin and P A H clearances are difficult to perform and require special laboratory facilities Their interpretation in disease is uncertain and this is made even more difficult by the demonstration by the Oxford workers of a circulatory shunt within the kidney They are therefore little used in clinical medicine but are of value in *elucidating the physiology of the normal kidney*

For the assessment of renal disease we depend upon the urea clearance and upon observations on the urine —on the presence of abnormalities such as albumin and casts or on alterations in its quality and quantity *One of the characteristics of the healthy kidney is its elasticity of function* In hot weather or when fluid is withheld a small quantity of highly concentrated urine is passed In cold weather or when a lot is drunk a large quantity of dilute urine is passed When the kidneys are diseased this adaptability is lost To get rid of the waste products a large volume of urine is passed with a specific gravity which becomes fixed at about 1010 With gross disease even this is insufficient to get rid of the waste materials which accumulate in the body Two tests which demonstrate the loss of elasticity of function are the Specific Gravity Test and the Water Elimination Test

Specific Gravity Test (Concentration Test) The patient should have nothing to drink after his mid day meal on the day before the test A dry supper should contain plenty of protein and breakfast too should include a meat dish but nothing to drink The patient empties his bladder on retiring and this specimen is discarded On waking he immediately passes water and again *one hour and two hours* later

All three specimens are carefully measured and their specific gravity determined For this purpose the graduated enamel jugs found in most wards in the country are useless and a glass measuring cylinder may have to be obtained from the laboratory Similarly the average hydrometer is far too inaccurate These are usually clumsy instruments reading in small divisions up to 1060 It is time that more delicate ones, reading only between 1010 and 1030 but in large divisions were generally adopted

If renal function is intact then the specific gravity of one or more of the three specimens passed should exceed 1020 A failure to concentrate to this figure shows a considerable impairment of renal function

Water Elimination Test (Dilution Test) This is best done with the patient under basal conditions so that errors due to the consumption of a large meal or drink prior to the commencement of the test are avoided The patient empties his bladder and is then given 1 200 cubic centimetres of water to drink in half an hour For the succeeding four hours he passes urine hourly The quantity and specific gravity of each specimen is measured carefully

A healthy individual will eliminate the extra water taken within *two or at the most four hours It will be found that the specific* gravity of the largest specimen passed is about 1002 With impairment of renal function both the quantity of urine is greatly decreased and the specific gravity becomes fixed at about 1010 Misleading results may be obtained if there is any myocardial weakness or generalised œdema

Serial urea clearance tests are of value as a demonstration of the downward trend of a case of nephritis but too much should not be read into a single examination Indeed, the interpretation of all the tests of renal function must be made with caution and they must always be correlated with the symptoms and clinical condition of the patient It will have been seen that in each of the tests described the kidneys are made to perform a maximum effort Thus a great deal of protein is given with a minimum of fluid or a large draught of water is given so as to produce a maximal diuresis Because they do not satisfy these exacting conditions it does not necessarily mean that the kidneys cannot deal with the ordinary demands made upon them by everyday life especially if these are modified by the imposition of a strict therapeutic regime The fact that a patient with Bright s disease has to get up once or twice at night to micturate may be of much graver significance than the fact that his urea clearance may have dropped from 55 per cent to 45 per cent

Finally, in assessing the prognosis of a case of nephritis from a consideration of the tests of renal function the time factor must be

borne in mind A patient with a rapidly progressing nephritis which reduces his clearance to 20 per cent within a few months is in a much worse plight than the one whose disease may have taken some years to reduce renal function to the same degree The one may be in coma the other still carrying on a sedentary occupation

Some of the possibilities that may result from the investigation of a case of renal disease by these tests are shown in *Table IV*

Table IV
Renal Function Tests

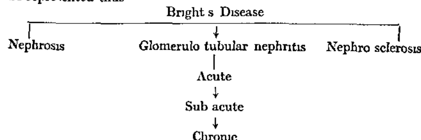
Concentration Test	Dilution Test	Blood Urea	Description	Example
Poor	Poor	Normal	Compensated Renal Disease	Chronic glomerular nephritis Renal arteriosclerosis Pyelonephritic contracted kidney
Poor	Poor	Raised	Uncompensated Renal Disease	Uræmia
Good	Poor	Raised	Diminished Glomerular Function	Acute nephritis Pre renal azotæmia

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NEPHRITIS

Classification

The classification of diseases which may lead to renal failure has always been a debatable subject A scheme which satisfies both clinicians and pathologists has been difficult to evolve one which commanded a good deal of support and which had the additional merits of being simple and practicable was given by Volhard It may be represented thus —



Recent research, however, calls for some reconsideration of this simple plan Ever since Bright s original description of the disease and his conception that hypertension was caused by renal disease attempts have been made to cause an increase in blood pressure by interfering with the kidney Many methods were tried but none was entirely successful until in 1934 Goldblatt Lynch Hanzal and Summerville succeeded in producing persistent hypertension in dogs by partially occluding one renal artery by means of a silver clip after the opposite kidney had been removed In 1939, *an important extension of this* work was made by Wilson and Byrom who showed that in rats sustained hypertension could be produced by the clamping of one renal artery without removal of the other kidney Pathological changes occurred in the untouched organ but the ischæmic kidney appeared to be protected from the high blood pressure which was produced These pathological changes were similar to those seen in malignant hypertension in man Later (1941) these same workers adduced evidence to show that once established hypertension could produce pathological changes in the kidneys and they showed that what has long been called ' chronic interstitial nephritis ' is not due to inflammation but to hypertension There exists a vicious circle in nephritis—renal disease leading to hypertension, which in its turn leads to further renal impairment

An account of the new conception of nephritis which follows from Goldblatt s (1934) work was given by Ellis in his Croonian Lectures for 1941 In this he makes two important statements The first is that what are known as acute and sub acute nephritis are two separate diseases, and the second that lipoid nephrosis does not exist as a separate entity but is always due to sub acute nephritis These conclusions are drawn from precise and prolonged observations on over 600 cases followed often for more than 20 years they are not the result of undocumented clinical impressions and must therefore be given close consideration The existence of lipoid nephrosis has been questioned by many authorities but it has always been held to be an excessively rare disease and though Ellis and his colleagues have met with no examples in their 600 cases this does not rule out the possibility of its existence The cases for instance reported by Bennett Dodds Robertson and Baker (1931) appear to be well authenticated

That the two conditions which are commonly given the names acute and sub acute nephritis are separate diseases and not two stages in the same disease is a much more novel suggestion Ellis holds that acute nephritis is a self limited disease influenced by treatment if this is commenced early enough and having almost always an excellent prognosis This statement is at variance with the findings of other workers—*for* instance Payne and Illingworth (1940) but weight is

given to Ellis theory by his comparison of the characteristics of the two diseases To avoid confusing the nomenclature of nephritis still more Ellis refers to them as nephritis Type I and Type II They are compared in the following Table V

Table V
Clinical Features of Nephritis (Ellis 1942)

	Type One	Type Two
Onset	Abrupt	Insidious
General Symptoms	Present	Absent
Hæmaturia	Present	Absent or slight
History of previous infection	In 84 per cent	In less than 5 per cent
Œdema	Short Duration	Persistent
Age of Incidence	60 per cent in first two decades	Relatively equally distributed in all decades
Recovery	82 per cent	Less than 5 per cent

Support for this view has been given by Davson and Platt (1949) in a clinical and pathological review of 188 cases of renal disease 45 of which were examples of Type I or Type II nephritis They conclude that the Ellis classification is sound in practice and leads in the great majority of cases to clinical and pathological agreement Roscoe (1950) examined the biochemical changes in the two diseases and found marked differences between them In Type I nephritis water is in excess both in the tissues and in the blood with resulting dilution of the constituents of the blood In Type II nephritis even though the œdema is considerable there is no such dilution

The different diseases of the kidney in their early stages produce well recognised clinical pictures If however they are extensive or progress so that renal failure is established there is produced the *composite picture of terminal Bright s disease It is not* proposed to describe all the various forms of nephritis in any further detail but mention will be made of two—malignant hypertension and terminal Bright s disease

Malignant hypertension was first described by Volhard in 1914 but it has come into prominence again owing to the researches of Wilson and Byrom (1941) who found that by clamping one renal artery in rats they could produce pathological changes similar to those seen in malignant hypertension in humans The particular lesion is a necrotising arteriolitis which occurs not only in the kidney but also in organs such as the pancreas and alimentary tract

Recent research, however calls for some reconsideration of this simple plan Ever since Bright's original description of the disease and his conception that hypertension was caused by renal disease, attempts have been made to cause an increase in blood pressure by interfering with the kidney Many methods were tried but none was entirely successful until in 1934 Goldblatt, Lynch Hanzal and Summerville succeeded in producing persistent hypertension in dogs by partially occluding one renal artery by means of a silver clip, after the opposite kidney had been removed In 1939, an important extension of this work was made by Wilson and Byrom who showed that in rats sustained hypertension could be produced by the clamping of one renal artery without removal of the other kidney Pathological changes occurred in the untouched organ, but the ischæmic kidney appeared to be protected from the high blood pressure which was produced These pathological changes were similar to those seen in malignant hypertension in man Later (1941) these same workers adduced evidence to show that once established, hypertension could produce pathological changes in the kidneys and they showed that what has long been called "chronic interstitial nephritis is not due to inflammation but to hypertension There exists a vicious circle in nephritis—renal disease leading to hypertension which in its turn leads to further renal impairment

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the disease is progressing rapidly then there may be uræmia with only a moderate rise of the blood urea, if however the renal failure is due to a slowly progressing glomerulo tubular nephritis then the blood urea may be well over 400 milligrams per 100 millilitres with only mild clinical uræmia The alkali reserve is lowered and the tetanic *symptoms are explained by a decreased blood calcium* Renal function tests show that both the power of concentration and of water elimination are greatly diminished In severe cases intravenous pyelography may not show any kidney shadows at all Clearance tests give an arithmetical symbol to a function the deficiency of which is only too apparent An electrocardiogram may show changes due to *myocardial damage*

The final termination of the disease may be marked by convulsions distressing to both the patient and his attendants or the more fortunate of these unfortunate individuals will drift into unconsciousness with steadily increasing nitrogen retention

This then is the picture of renal failure seen most commonly in glomerulo tubular nephritis but possibly caused by one of several other conditions It will be appreciated that a scheme such as was given at the beginning of this section does not cover all the possibilities It makes no allowance for instance for those cases which appear to be classical examples of chronic nephritis but which are cured by the removal of a unilateral hydronephrosis (Hardwick and Badenoch 1947) It will have to be replaced by a catalogue of disorders some widely dissimilar in their ætiology but all similar in that they lead to a destruction of nephrons with consequent abolition of their function Such a catalogue is given in Table VI

Table VI
Bright s Disease

Underlying Cause	Example
Inflammation	Acute sub acute or chronic nephritis
Infection	Chronic pyelonephritis
Degeneration	Lipoid Nephrosis amyloid disease
Vascular	Malignant hypertension rarely benign hypertension
Circulatory upset	Tubular nephrosis cortical necrosis
Surgical kidney	Hydronephrosis etc
Congenital defect	Polycystic disease hypoplastic kidney
Due to other diseases	Bacterial endocarditis polyarteritis nodosa

In the abruptness of its onset and the rapidity of its downhill course malignant hypertension behaves as a separate disease Its prognosis is so poor that its recognition is important though Platt (1948) suggests it is one subdivision of hypertension Platt has shown that malignant and benign hypertension have a similar hereditary background and age incidence and a transition from one to the other may sometimes be seen Further, a hypertension secondary to some such cause as chronic pyelonephritis may undergo a malignant termination This is not a disorder of young people, the average age of Platt's cases was 47 years Headaches failure of vision, and convulsive seizures may be the first symptoms There may be no complaint of renal symptoms, but cross examination will usually reveal thirst and polyuria due to failure of the concentrating power of the kidney On clinical examination the salient findings are an extreme degree of hypertension the diastolic usually being over 140 millimetres papillœdema and albuminuria Laboratory investigations will show nitrogen retention and impairment of renal function Death follows within a few months of the diagnosis being made and is never delayed for more than two years

Terminal Bright s disease may offer no clues as to its correct ætiological diagnosis This may only be possible after death when the history and clinical findings can be correlated with the morbid histology

Symptoms may be due either to hypertension or to uræmia, or to a combination of the two Thus there may be severe headaches with *visual disturbances and convulsive seizures or there may be increasing* restlessness and weakness followed by vomiting and drowsiness Occasionally left ventricular failure or even a cerebral hæmorrhage may mask the underlying renal disease

The patient is wasted and dehydrated with a sallow complexion There is marked anæmia and a dry furred tongue The arteries are thickened and tortuous, and the blood pressure greatly increased The heart is enlarged and there may be an apical gallop rhythm or pulsus alternans both signs of the utmost gravity Pulmonary œdema may provide further evidence of left ventricular failure Abdominal examination is usually negative but polycystic kidneys or a large hydronephrosis may be palpable and gross constipation may lead to a heavily over loaded colon The tendon reflexes may be exaggerated and signs of tetany may be found The urine always contains albumin, though the amount may not be great it is dilute and as the patient's condition deteriorates so the specific gravity becomes fixed at about 1010 There are casts and red cells in the deposit Finally there is a severe hypertensive retinopathy with exudates hæmorrhages and papillœdema

Laboratory investigations reveal nitrogen retention but the degree of this does not necessarily reflect the severity of the symptoms If

the disease is progressing rapidly then there may be uræmia with only *a moderate rise of the blood urea if however the renal failure is due* to a slowly progressing glomerulo tubular nephritis then the blood urea may be well over 400 milligrams per 100 millilitres with only mild clinical uræmia The alkali reserve is lowered and the tetanic symptoms are explained by a decreased blood calcium Renal function tests show that both the power of concentration and of water elimination are greatly diminished In severe cases intravenous pyelography may not show any kidney shadows at all Clearance tests give an arithmetical symbol to a function the deficiency of which is only too apparent An electrocardiogram may show changes due to myocardial damage

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Congenital defect	Polycystic disease hypoplastic kidney
Due to other diseases	Bacterial endocarditis polyarteritis nodosa

Treatment

Ellis (1942) considered that Type I or acute nephritis, usually responds completely to treatment provided that this is instituted early. This does not mean, however, that there is any new and strikingly successful way of dealing with this disease. Rest, both of the body and of the kidneys, remains the sheet anchor. The patient should be kept in bed until recovery has occurred or the acute phase is over; the kidneys are given as little work to do as possible by restricting food and liquids to a minimum. An apple or an orange each day is all the solid food that should be allowed and only enough fluid to prevent thirst should be given. This can usually be done on one pint a day but in hot weather a more generous ration may be permitted. This strict regime can be kept up for as long as a week, by which time the acute symptoms will usually have subsided and a more liberal diet can be allowed, but proteins must be restricted until the urine is clear and the blood urea normal.

In severe cases of acute glomerulo tubular nephritis, particularly when vomiting is a leading feature or when the urinary output is very reduced, treatment should be by means of an intragastric drip as described by Bull, Joekes and Lowe (1949) in cases of anuric uræmia. This method (see p. 184) may also be used for patients with chronic renal failure who have an acute exacerbation. In such patients, however, the treatment is only a temporary measure and no permanent improvement in renal function can be expected.

In view of the close association between streptococcal infections and acute nephritis, Moncrieff (1944) suggested that penicillin might be a valuable therapeutic agent and he was able to quote an example which appeared to support this contention. Subsequent experience has proved disappointing—too often the streptococcal infection has burnt itself out before the nephritis appears. No large and carefully controlled series has yet been reported, however, and until this has been done judgment cannot be passed. Certainly penicillin is preferable to the sulphonamides, any of which may cause anuria even in individuals whose kidneys appear to be healthy.

Sub acute nephritis, or Type II, remains a disease the downward course of which is little altered by treatment. There was some hope that the œdema might be controlled by the transfusion of a concentrated serum which would restore the depleted serum proteins to normal. This is not so. Brown, Gray and Mollison (1942) reported their experiences with 12 œdematous patients who were treated with concentrated serum transfusions containing from 20–100 grams of protein; two only were completely relieved of their œdema and in one of these it returned within ten days. The added protein does not stay in the circulation for any length of time and, furthermore, it is possible

that the salt in the serum counteracts any benefit that might come from the protein Evidence is accumulating that Epstein s theory that the low plasma proteins in this condition are due entirely to the albuminuria requires modification but no satisfactory alternative explanation can yet be offered

In the absence of any advance in treatment the œdema has to be dealt with by old fashioned methods Mercurial diuretics such as mersalyl are usually contra indicated but great relief may always be obtained by incising the legs of these patients This is such a simple procedure and its value may be so great that it should be more widely adopted The dangers of infection have always been thought to militate against it but these are not great these days For a few days before the operation the patient should be nursed in a sitting position either in a chair or in a cardiac bed When the anasarca has drained to the most dependent parts the fluid may be released by small incisions not more than half an inch long through the skin of the dorsum of the feet made under local anæsthesia from an ethyl chloride spray The whole procedure must be done under the most strict aseptic precautions which must be kept up all the time that drainage goes on and dressings may have to be changed every hour

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ACUTE URÆMIA

Clinical Features

(Renal failure after injuries surgical operations and other diseases)

Uræmia is a condition characterised by a disorder in the biochemistry of the body It occurs most commonly as a terminal event in Bright s

disease, in such cases its symptomatology is often obscured by the presence of other disorders, notably hypertension So called uræmic convulsions for instance are due to hypertensive encephalopathy and not to any biochemical upset The name uræmia is a time honoured one it suggests that an increase in the blood urea is the all important change Certainly a high blood urea always occurs but that this is necessarily injurious has always been questioned Recently more and more attention has been paid to other biochemical derangements—to reduction in the alkali reserve, to chloride depletion and, perhaps most important of all potassium retention

Pure uræmia where the symptoms due to the biochemical changes are not confused by those due to hypertension and other disorders occurs as an acute episode in a variety of conditions These include severe injuries crushing major surgical operations, mis matched transfusion sulphonamide sensitivity, and diseases such as Addison s disease alkalosis and diabetic coma A syndrome which is clinically similar occurs after concealed antepartum hæmorrhage and other obstetrical emergencies A variety of names have been given to the condition—pre renal azotæmia pigment nephrosis transfusion kidney crush syndrome traumatic uræmia or anuria, tubulovascular renal syndrome and renal anoxia syndrome

The clinical picture is characteristic After a severe injury or operation at the height of a disease in which there is a period of hypotension and circulatory failure or after a concealed antepartum hæmorrhage the patient s condition begins to deteriorate Drowsiness and apathy supervene nausea and anorexia are followed by hiccoughs and vomiting and the urinary output steadily diminishes until there may be complete anuria Biochemical studies show a lowered alkali reserve and chloride with a raised potassium and a great increase of urea in the blood Death occurs in a large percentage of the cases but recovery when it occurs appears to be complete this is in sharp contrast with other forms of nephritis

Morbid anatomical studies show that there are two distinct patho logical pictures In one so called tubular nephrosis the greatest changes occur in the ascending loops of Henle and in the second convoluted tubules in the other changes are almost confined to the glomerular layer and there is a bilateral cortical necrosis of the kidneys

In tubular nephrosis the kidneys are slightly enlarged and there is a striking contrast between the pale cortex and the congested medulla Microscopically the glomeruli which are relatively normal lie in an avascular area There is necrosis of the tubules the degenerate epithelium of which is stripped from its basement membrane and lies free in the lumen In other places the tubules are filled with pigment casts which may be formed around a nidus of sulphonamide crystals or

cellular debris Some of the tubules may be seen to have ruptured into the neighbouring vascular spaces or into the interstitial tissue

In bilateral cortical necrosis by contrast the damage is not confined to one specific region of the individual nephrons but a large anatomical division of the whole kidney is affected In the cortex all elements vessels glomeruli and convoluted tubules become necrotic As a rule this necrosis involves the whole cortex but some cases have been described in which the changes were confined to scattered areas

The biochemical changes which occur in both these conditions are striking and a knowledge of them is important The blood urea rises to levels of 700 milligrams per 100 millilitres and over Hypochloræmia and a low alkali reserve are usual The blood potassium is increased and in some patients may be responsible for ventricular fibrillation and death Any urine that is passed is dilute with a specific gravity fixed between 1014 and 1018 Despite the high blood urea the urine urea seldom rises above two per cent The urine is always acid and although the alkali reserve may be restored to normal there is a lag in the reaction of the urine which may not become alkaline for several days Treatment must therefore be controlled by repeated estimations of the alkali reserve and not by observations on the reaction of the urine alone (Darmady 1947)

In bilateral cortical necrosis of the kidneys there is such extensive damage to so vital a part of the kidneys that recovery probably never takes place Where the lesions are patchy the patients may survive but unless the kidneys themselves are seen during the illness it is impossible to be certain that the lesion was cortical necrosis and not tubular nephrosis In the latter condition however repair processes start early At autopsy in cases surviving for any length of time a considerable degree of regeneration is always present Another encouraging feature is that when recovery does take place it is always complete

Ætiology The ætiology of this condition is still uncertain but much progress is being made towards its elucidation Maegraith and others (1945) considered three possibilities —

(1) Mechanical blockage of the tubules

(2) A nephrotoxic effect of some injurious substance carried to the kidney by the blood stream

(3) Renal anoxia the main cause of renal damage being the temporary deprivation of oxygen

The first hypothesis was originally put forward by Baker and Dodds (1925) to explain the anuria in mismatched transfusions Bywaters (1948) suggests that in both this condition and in the crush syndrome there is a precipitation of pigment on the walls of the distal tubules as a result of which there is a failure of absorption of the glomerular filtrate

The subsequent increase in pressure causes distension and rupture of the tubules. The deposition of pigment, however, is not seen in every tubule; still less is every tubule blocked by pigment or crystals. The second theory is also difficult to accept. The variety of conditions which may be followed by the syndrome means that either the same toxin must occur in widely different disorders or there must be many different toxins having the same effect. No such agent has yet been identified in any of the disorders mentioned.

The theory of renal anoxia has gained considerable support from the work of Trueta and his colleagues (1946, 1947). In the course of experiments designed to show whether a vascular disturbance originated by reflexes from a damaged limb played any part in the production of the renal changes found in the crush syndrome, these workers discovered that there are two alternative circulations in the kidney. The one pathway lies within the medulla, the other in the cortex; blood may flow exclusively through either route or flow in varying amounts through each of them. To traverse the medullary route the blood leaves the interlobular arteries by the afferent arteries of the juxta-medullary glomeruli, and after passing through these *glomeruli it is directed via the vasa recta to the interlobular veins.* For the cortical route the blood remains in the interlobular arteries *until it reaches the afferent vessels of the remaining* cortical glomeruli. It goes through these into their efferents, to the cortical *intertubular network and thence to the interlobular veins.* Here the *two circulations reunite and the mixed blood passes on to the main vein.*

In their experiments the Oxford workers found that constriction of *the cortical circulation and opening* of the medullary route followed the application of a tourniquet to one hind limb of an anæsthetised *rabbit. As they pointed out this change may* well be enhanced in injured humans who have the additional emotional strain of wounding; *in both cases the pathological* changes are fundamentally similar. If the shunt, besides being invoked by neuro-vascular reflexes, has the aim of protecting *glomeruli from* toxins or of reducing glomerular function so as to conserve body fluid, then the production of similar pathological changes in such widely divergent conditions as crushing injuries, mismatched transfusions and dehydration becomes understandable. On this theory bilateral cortical necrosis provides the most striking example of the diversion of blood flow within the kidney from cortex to medulla. Nevasquez (1938) considered that vascular spasm played no part in the production of this condition and showed that the cortical vessels are dilated and not contracted. Trueta points out, however, that such dilatation may well be due to vasoparalysis following a *period* of severe vasospasm.

Treatment There are three possible methods of approach to the treatment of these forms of acute uræmia As a prophylactic measure there must be vigorous resuscitation during the shock and dehydration which so often precedes the anuria Trueta and his colleagues (1947) have shown that the circulatory shunt in the kidney is not provoked if the splanchnic nerves are cut though this is not to say that once established the shunt will be abolished by paralysis of the splanchnic nerves Further if the shunt has been in action for sufficient time for structural damage to have occurred in the kidney its reversal is unlikely to be followed by clinical improvement Nevertheless a splanchnic block has been used successfully by Darmady (1947) though Porritt (1945) found it of little value Tetræthyl ammonium bromide was used by Stock (1948) in cases of pre eclampsia but there was no lasting benefit

The temporary nature of this form of renal failure and the completeness of the recovery when it does occur have been stressed Unfortunately the cessation of kidney function is frequently so complete that death occurs before the repair is sufficiently advanced to enable the secretion of urine to be resumed Attempts have been made therefore to arrange for the excretion of waste products urea in particular by other routes so that life can be prolonged until the kidneys resume their work

Dialysis of the blood has been suggested by several workers and the first practicable artificial kidney was devised by Kolff in 1946 and in this country Darmady (1948) and Bywaters and Joekes (1948) have described similar pieces of apparatus Under full doses of heparin the patient s blood is led from the radial artery into a cellophane tube 5 cm in diameter and 30–45 metres long and thence back into a vein The cellophane tube is wound round a drum which rotates in a bath containing 70–100 litres of a modified Ringer s solution Urea is not the only substance which is dialysed and frequent estimations have to be made of all the electrolytes in the blood Dialysis is only continued for a few hours at a time but even so large quantities of urea can be extracted from the blood and Kolff has removed as much as 263 g Unfortunately water passes into the blood stream and death from left ventricular failure some time after dialysis has been completed is not uncommon

Peritoneal dialysis and the perfusion of loops of small intestine are other methods by which metabolites may be removed from the blood The former has been described by Frank (1946) and in this country has been used by Reid Penfold and Jones (1946) There is a risk of peritonitis and the catheters through which the irrigating fluid is introduced and collected may become blocked by omentum though this can be avoided by using stainless steel tubes About 40 litres of

The subsequent increase in pressure causes distension and rupture of the tubules The deposition of pigment, however is not seen in every tubule still less is every tubule blocked by pigment or crystals The second theory is also difficult to accept The variety of conditions which may be followed by the syndrome means that either the same toxin must occur in widely different disorders or there must be many different toxins having the same effect No such agent has yet been identified in any of the disorders mentioned

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attracted from the cells This osmotic upset is probably responsible for the final death of the patient The patient becomes weak and listless and complains of thirst which becomes progressively more intense as the condition is allowed to progress The mouth and tongue become parched and leathery the patient is grey and pinched and may suffer from confusion and hallucinations The urinary output is reduced to a minimum but its chloride content is not reduced and in the early stages may even be increased

In pure salt depletion the extracellular fluid becomes hypotonic with the result that water is attracted from it into the cells and is removed from it by the kidneys There is thus a reduction of the plasma volume with the production of oligæmic shock The patient becomes increasingly apathetic and complains of muscular weakness headaches giddiness and cramps Thirst however is notably absent Vomiting leads to a further loss of chlorides in the gastric juice Finally peripheral circulatory failure occurs and may lead to death For a time the volume of the urinary output is maintained but it is increasingly *deficient in chlorides*

Thus it is possible for a patient to be dangerously dehydrated and *yet not be thirsty and to be passing plenty of urine* As Marriott *points* out when the state of hydration of a patient is in question 24 hours *is too long a time to allot for a review of the urinary output* The volume passed and its chloride content should be checked every eight *hours the aim of treatment being to ensure that the patient passes a* pint (570 ml) of urine in this time containing 3–5 g per litre of sodium chloride

It is almost a tradition that before an operation a patient s urine is *tested for albumin and sugar It should become equally traditional* that in the days immediately after any major operation every specimen *passed besides being measured should have its chloride content* estimated

Treatment consists of giving salt and water in adequate amounts If it is at all possible this should be given by mouth If the patient *cannot swallow a small plastic stomach tube can be passed through* the nose and the solution dripped into the stomach In severe salt *deprivation the rapid intravenous transfusion of isotonic (0 85* per cent) saline solution may be life saving but in the ordinary course of events Marriott *recommends the use of a hypotonic solution made by mixing* equal quantities of isotonic saline and isotonic glucose (5 per cent) solutions (See also Chapter IV)

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dialysing fluid have to be used each day and the patient may develop pulmonary œdema

Bull Joekes and Lowe (1949) emphasise the importance of depressing exogenous protein metabolism to a minimum and of maintaining mineral and water balance Borst (1948) showed that a diet containing practically no protein or potassium reduced protein katabolism in three days to six grams of nitrogen The diet used consisted of butter and sugar a very unpalatable mixture Bull and his colleagues recommend the following mixture —

Glucose	400 g
Peanut oil	100 g
Acacia q s to emulsify	
(Vitamins optional)	
Water to 1 litre	

This is the day s ration and it is dripped into the stomach throughout the 24 hours by means of a plastic tube passed through the nose All vomit is collected and returned through the stomach tube after filtration This is an important measure for it ensures that the fluid intake is accurate and that no food or electrolytes are lost in the vomit By this means serious upset of electrolyte balance may be avoided during the period of anuria Once diuresis starts however electro lytic imbalance readily occurs and losses of particular electrolytes will have to be made good This does not mean that massive saline or alkaline transfusions can be started The daily fluid requirements are no more than the litre of water in the above prescription with an additional amount equal to the volume of the urine passed the previous day

The dangers of over transfusing these patients cannot be emphasised too strongly Drip methods of transfusion have saved countless lives but they must also have been responsible for the deaths of innumerable anuric patients There is no place for the use of large quantities of intravenous saline or glucose saline let alone hypertonic glucose and sodium sulphate solutions

The whole subject of water balance was considered by Marriott in his Croonian Lectures to the Royal College of Physicians in 1946 He showed that dehydration may occur owing to a lack of water or to a loss of chloride In practice both are usually present but the principles of treatment can best be understood by considering the two syndromes separately

The fluid content of the body is divided between a large intracellular component and a smaller extracellular component This latter comprises the plasma and the tissue fluid The intracellular fluid contains most of the sodium chloride and bicarbonate in the body

When a patient loses or is deprived of adequate amounts of water the extracellular component becomes hypertonic and so water is

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Urinary infections in children are common and their response to the sulphonamides is so striking that Sheldon (1945) suggests that there may be a danger in routine chemotherapy The urine may be sterilised despite stasis in the urinary tract and unless a pyelogram is done on every child anatomical abnormalities may be missed This is an impracticable and unjustifiable procedure in children and Sheldon therefore advocates initial alkaline treatment Potassium citrate may be used for an infant the dose is 10 grains and for an older child 20–30 grains It must be given two hourly by day and three hourly by night and fluids must be given in large quantities The urine must be made alkaline not neutral and each specimen passed should be tested with litmus paper which can be included in an infant s napkins Sheldon claims conspicuous success for this treatment if it is given efficiently Failure suggests stasis or atony in the renal tract and the sulphonamides or an antibiotic may then be used The dose of sulphadimidine should be 0 25 gram eight hourly in the first year 0 25 gram six hourly from one to seven years and 0 5 gram eight hourly from seven to ten years In each case the initial dose must be double When the urine has been sterilised a complete urinary investigation should be carried out on each of these children

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of our teaching Sterile pyuria, however may occur apart from tuberculosis and a definite clinical entity known as *Abacterial Pyuria* has been described It has been suggested that the condition may be due to a virus infection (Moore, 1943) to the excretion of toxins from a focus elsewhere in the body (Cooke, 1944) or to an organism of the spirochætal group (Peters 1946) Its recognition is important because it responds rapidly to arsenical treatment

The syndrome occurs more commonly in men than in women and though the symptoms are usually severe, the patient s general condition is unaffected There is neither fever nor loss of weight, but frequency may be extreme hypogastric or perineal pain severe and hæmaturia common In men a purulent urethritis may precede the urinary symptoms and the two glass test shows an equal haze in both specimens Cystoscopy shows a markedly irritable and contracted bladder the mucosa of which is uniformly reddened and even ulcerated It is possible that some cases of Hunnah s Ulcer may be examples of this syndrome Pyelography may be normal but blunting of the calyces is common The changes are not necessarily bilateral and may be confined to one side or may be more marked on one side than the other The differentiation from tuberculosis in these cases is especially difficult

Treatment by means of the intravenous injection of one of the preparations of neoarsphenamine is dramatic and complete The dose need not be large and it is usual to give a course of four injections of 0 3 gram of N A B at intervals of from four days to a week

During the investigation of such a case tuberculosis must always be uppermost in the mind of the physician and every effort must be made to isolate the tubercle bacillus In suspected patients the therapeutic trial of N A B is well worth while but in doing so the rarity of the condition must be remembered—Moore (1943) found only five examples in 80 cases of pyuria and the response to treatment must be considered in a coldly critical light The symptoms must go completely and there should be no relapse In some cases a streptococcus may be recovered from the urine immediately after the cessation of treatment but this appears to be a transient finding of uncertain significance

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THE RENAL ASPECTS OF HYPERTENSION

In 1827 Richard Bright drew attention to the association of albuminuria contraction of the kidneys and hypertrophy of the heart For some time after this it was accepted that hypertension was always due to renal sclerosis In 1881 Mahommed described the occurrence of high blood pressure in individuals who showed no evidence of kidney disease and so paved the way for Sir Clifford Allbutt s work on hyperpiesia The pendulum then swung the opposite way and it was taught that there was little connection between hypertension and the kidney In part this change in opinion was due to a failure to produce hypertension in animals by operations on the kidneys although many methods often involving severe injuries or the injection of different toxic substances were tried

In 1934 Goldblatt Lynch Hanzel and Summerville showed that constriction of both renal arteries in dogs was followed by hypertension which persisted for 15 months or more A further step forward was taken by Wilson and Byrom (1939) when they showed that in rats constriction of one renal artery was followed by hypertension and pathological changes in the unclamped kidney indistinguishable from those of malignant hypertension in man There followed a further swing of the pendulum and by 1938 American workers were advocating that all people with hypertension should undergo a full urological investigation so that a unilateral renal lesion should not be missed But examples of hypertension which can be relieved by the removal of an abnormal kidney are extremely rare Braasch (1942) estimated that out of approximately 4 000 cases of hypertension seen at the Mayo Clinic only 19 were suitable for nephrectomy he puts the general incidence of such cases at only a fraction of one per cent Even if one abnormal kidney should be discovered in association with hypertension it does not follow that its removal is to be recommended without further thought Each case must be carefully and fully investigated and the most rigid criteria must be satisfied These have been laid down by Sensenbach (1944) and Wilson (Bennett Wilson and Lockett 1945) The patients should be young for over the age of 50 years hypertension is much more likely to be permanent The function of the damaged kidney must be nil whilst that of the healthy one must be normal when judged by the most searching tests If this is not so then the removal of a damaged but still secreting organ may put such an extra strain upon the remaining slightly defective kidney that it too will fail and uræmia may be precipitated The only exception to this rule is the malady known as malignant hypertension This is a fatal condition and the discovery and removal of a unilateral renal lesion may provide the only hope of recovery It may occasionally be successful (Hardwick and Badenoch 1947)

of our teaching Sterile pyuria, however may occur apart from tuberculosis and a definite clinical entity, known as *Abacterial Pyuria* has been described It has been suggested that the condition may be due to a virus infection (Moore 1943) to the excretion of toxins from a focus elsewhere in the body (Cooke 1944) or to an organism of the spirochætal group (Peters, 1946) Its recognition is important because it responds rapidly to arsenical treatment

The syndrome occurs more commonly in men than in women and, though the symptoms are usually severe, the patient s general condition is unaffected There is neither fever nor loss of weight, but frequency may be extreme hypogastric or perineal pain severe and hæmaturia common In men a purulent urethritis may precede the urinary symptoms and the two glass test shows an equal haze in both specimens Cystoscopy shows a markedly irritable and contracted bladder the mucosa of which is uniformly reddened and even ulcerated It is possible that some cases of Hunnah s Ulcer may be examples of this syndrome Pyelography may be normal but blunting of the calyces is common The changes are not necessarily bilateral and may be confined to one side or may be more marked on one side than the other The differentiation from tuberculosis in these cases is especially difficult

Treatment by means of the intravenous injection of one of the preparations of neoarsphenamine is dramatic and complete The dose need not be large and it is usual to give a course of four injections of 0 3 gram of N A B at intervals of from four days to a week

During the investigation of such a case tuberculosis must always be uppermost in the mind of the physician and every effort must be made to isolate the tubercle bacillus In suspected patients the therapeutic trial of N A B is well worth while but in doing so the rarity of the condition must be remembered—Moore (1943) found only five examples in 80 cases of pyuria and the response to treatment must be considered in a coldly critical light The symptoms must go completely and there should be no relapse In some cases a streptococcus may be re covered from the urine immediately after the cessation of treatment, but this appears to be a transient finding of uncertain significance

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How does the constriction of one renal artery produce *hypertension?* An easy explanation is that the increased pressure is necessary to maintain the circulation in the kidney beyond the clamp. But as Goldblatt and others (1934) point out this is a teleological argument and is unconvincing. We do not know that the intra renal pressure is maintained or indeed, that its maintenance is essential. Page (1943) asserts that it is not. The clamps produce their effect independently of the nervous system, for hypertension follows if they are applied to the artery of a normal kidney, a denervated kidney or a denervated kidney transplanted to the neck of the same or another animal (Blalock and Levy, 1937). Goldblatt concludes that the increased blood pressure is due to a toxic substance which is produced in the kidney by an alteration in its metabolism.

This suggestion has caused a revival of interest in some observations made nearly 50 years ago. In 1898 Tigerstedt and Bergmann isolated a substance from the cortex of a normal kidney which was capable of producing hypertension and to which they gave the name of renin. For a long time little interest was shown in this material—perhaps as Pickering (Ellis, Wilson and Pickering 1942) suggests, because of the difficulties of its preparation its instability and the fact that its action is inhibited by most anæsthetics. Renin is an enzyme which acts upon a globulin fraction of the blood (hypertensinogen or angiotonin activator) to form a pressor substance (hypertensin or angiotonin) viz Renin + Hypertensinogen (Angiotonin activator) → Hypertensin (Angiotonin).

The intravenous injection of hypertensin results in an immediate but brief, rise in blood pressure. A similar injection of renin gives a slow rise which is maintained longer. Repeated injections of renin however are followed by a diminishing response and this renal tachyphylaxis as it is called suggests that renin is more concerned with the regulation of blood pressure than with its maintenance at a raised level (Bennett Wilson and Lockett 1945). Renin may initiate a rise in blood pressure its persistence appears to be due to other as yet undetermined factors (Pickering 1945).

Finally the intimate anatomy of the kidney must be considered. The renal arterioles are unique in two respects. First they possess a muscular sphincter which can control the blood flow through each glomerulus. Secondly there is a ready made collateral circulation in the tubular vascular network. The significance of these vessels is enhanced by the recent researches of Trueta and others (1946) who have shown that in certain conditions there may be an upset in the renal circulation in which the blood by passes the glomeruli and goes straight to the tubules.

One other anatomical feature of the kidneys is of importance. At

the root of each glomerulus in the angle formed by the afferent and efferent arterioles is an aggregation of cells formed partly by the altered endothelium of the second convoluted tubules and partly by the cells lining the afferent arterioles This aggregation is known as the juxta-glomerular complex (Goormaghtigh 1932) In certain disorders nephritis hypertension and the crush syndrome these cells become more granular (Goormaghtigh 1945) and to complete the picture there is evidence to show that they are the site of the production of renin (McManus 1942)

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CHAPTER VII

BLOOD DISEASES

by

M C G ISRAELS

The Hæmorrhagic Diseases Leukæmia Blood Groups and the Rh Factor Transfusion Substitutes Hypersplenism

THE HÆMORRHAGIC DISEASES

A great volume of research work on the coagulation of the blood has appeared in the last few years Much of it is still controversial, but it is now possible to apply some of it to a restatement of our ideas on hæmorrhagic diseases their ætiology and treatment The two main groups are still —(1) diseases associated with an abnormality of the blood clotting process and (2) diseases in which no abnormality of blood clotting can be detected the blood vessels being at fault

In order to understand and classify the first group it is necessary to consider briefly present day views on the steps of the blood clotting process At least five steps are now envisaged —

(1) Thromboplastinogen + Platelet factor → Thromboplastin

(2) Thromboplastin + Prothrombin + Calcium → Thrombin

(3) Plasma prothrombin accelerator $\xrightarrow{\text{thrombin}}$ serum prothrombin accelerator

(4) Prothrombin + Thromboplastin + Ca

$$\xrightarrow[\text{prothrombin accelerator}]{\text{serum}} \text{Thrombin}$$

(5) Thrombin + Fibrinogen → Fibrin

This is not a complete scheme for instance thrombin is known to have a labilising effect on platelets but it suffices for clinical purposes Those who wish to pursue the matter further should consult Macfarlane's (1948) review

Stage 1 It has been shown by several workers that in circulating blood there is a plasma factor which is inert until brought into contact with disintegrating platelets the platelets act on this plasma factor to produce an active thromboplastin and once this occurs the clotting process is set in action and stage 2 proceeds Quick (1947a) called this plasma factor *thromboplastinogen*

Stage 2 This is Morawitz's original first step and is a chemical reaction thus differing from the others which are enzymatic Stage 2 only proceeds slowly in the absence of prothrombin accelerators The prothrombin accelerators have been detected by various workers and given different names Frommeyer and Epstein (1949) introduced the apt term prothrombin accelerators

Stage 3 The prothrombin accelerator in plasma is relatively inert it is changed to the active serum form in the presence of thrombin So as soon as stage 2 produces some thrombin, stage 3 proceeds and all the inert plasma accelerator is rapidly converted into active serum accelerator (Seegers and Ware 1949) There is also evidence that thrombin hastens the disintegration of platelets and thus acts as an accelerator of stage 1

Stage 4 This is stage 2 proceeding much more rapidly to reach an end point when all the prothrombin is converted to thrombin in the presence of active serum accelerator factor

Stage 5 The classical conversion of fibrinogen to fibrin

It will be seen that in circulating blood the absent factors are the *platelet factor serum prothrombin accelerator thrombin* and of course *fibrin* One difficulty has been that since the final stage is enzymatic an excess of thrombin will be present In thrombosis a clot can form in an unruptured blood vessel and if thrombin is present in excess there seems no reason why all the circulating blood should not clot Quick (1950) has pointed out two ways in which this is prevented Firstly it has been shown that fibrin itself absorbs and temporarily inactivates thrombin as it is formed then when clot retraction recurs and the thrombin containing serum is expressed a good local blood flow ensures adequate dilution of the thrombin There also exist natural anti thrombins they are slow in action but must be reckoned with because some cases of hæmorrhagic disease are caused by excess of circulating anticoagulants

With the exception of syndromes due to circulating anticoagulant the hæmorrhagic diseases caused by defective blood clotting are all

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prothrombin concentration normal

Idiopathic cases

Cases after exposure to overdoses of radiation X rays or atomic explosions

(B) **Abnormality of Blood Vessels**

All blood investigations normal

(1) *Hereditary Hæmorrhagic Telangiectasia*

(2) Schonlein Henoch Syndrome

(3) Pseudo hæmophilia

(4) Nutritional purpura scurvy

(5) Symptomatic purpura *in infections and some skin diseases* e g Schamberg s disease

A (1) **Hæmophilia** There is now reasonably secure evidence that hæmophilia is caused by an hereditary absence of the factor Quick calls *thromboplastinogen* Consequently the whole blood clotting process is held up because though platelets are shed and disintegrate there is no plasma factor for the platelet enzyme to act upon and since no appreciable amount of thrombin is formed its accelerating action on platelet disintegration is absent and so the platelets appear abnormally stable Hæmophilic blood clots slowly because especially in glass tubes some thrombin is formed directly from prothrombin and so a clot of sorts forms But very little prothrombin is used up in the process and Quick has made this the basis of a valuable and specific test for hæmophilia In Quick s prothrombin consumption test as it is called the blood is allowed to clot and the prothrombin remaining in the *serum* is estimated After 24 hours for example the prothrombin time of the serum from normal blood is about 120 secs compared with the normal plasma value of about 12 secs —very little prothrombin is left In hæmophilic blood the prothrombin time of the serum may well be 15–20 secs indicating that very little prothrombin has been consumed The importance of the test is that it gives a clearly positive result with those hæmophilics whose blood coagulation time, by the usual methods is only slightly prolonged The only other condition in which low prothrombin consumption occurs is thrombocytopenic purpura when the platelets are very low —say 10 000 p c mm or so This would be expected from the reaction in stage 1 the platelet factor being diminished In hæmophilia the platelet count is normal so no confusion arises and in practice the diminution of prothrombin consumption in thrombocytopenic purpura is not as extreme as in hæmophilia The diagnosis of hæmophilia can now be made with considerable precision by the aid of this test together with the clinical and family history

The discovery that hæmophilia is due to the absence of a factor present in normal plasma has shown the way to rational therapy

due to deficiencies of one or other factor, and they can be classified accordingly The table shows a classification scheme and further details are given below

TABLE OF CLASSIFICATION OF HÆMORRHAGIC DISEASES

(A) Abnormality of the Blood Coagulation Process

(1) *Deficiency of plasma factor thromboplastinogen* —
Clinical tests coagulation time prolonged hardly any prothrombin consumption, normal plasma prothrombin concentration platelet count, and bleeding time
Hæmophilia

(2) *Deficiency of platelet factor* —
Clinical tests coagulation time normal prothrombin consumption diminished in severe cases platelet count low bleeding time prolonged plasma prothrombin concentration normal
Primary Thrombocytopenic Purpura
Secondary Thrombocytopenic *purpura due to blood diseases*, especially aplastic anæmia and acute leukæmia associated with pregnancy and menstruation
Secondary Thrombocytopenic Purpura due to drugs e g gold sedormid

(3) *Deficiency of prothrombin* —
Clinical tests plasma prothrombin concentration much diminished coagulation time normal or slightly prolonged bleeding time and platelet count normal
Congenital Hypoprothrombinæmia
Hæmorrhagic Disease of the Newborn
Other forms of vitamin K deficiency, nutritional liver disease salicylate treatment
Treatment with Dicoumarol or similar substances

(4) *Deficiency of plasma prothrombin accelerator factor* —
Clinical tests coagulation time prolonged Quick s prothrombin time prolonged special tests
Parahæmophilia

(5) *Deficiency of fibrinogen* —
Clinical tests coagulation time prolonged prothrombin plasma *concentration and platelet count normal* bleeding time may be prolonged special tests
Congenital Fibrinogenopenia
Constitutional Fibrinogenopenia

(6) *Presence of circulating anticoagulants* —
Clinical tests coagulation time prolonged patient s blood will prolong the coagulation time of normal blood plasma

splenectomy while hæmorrhages may continue unchecked The proportion of these resistant cases that are truly primary is probably not more than ten per cent but they are disconcerting and efforts have been made to detect them before splenectomy With this object in view the megakaryocytes of the bone marrow have been critically examined Dameshek and Miller described the occurrence of peculiar megakaryocytes with a basophilic non granular cytoplasm that they called lymphoid forms others have placed emphasis on the occurrence of early forms of megakaryocytes—normally very unusual in bone marrow smears—or in the presence of mature cells without the usual granule formation in the cytoplasm It has been suggested that unless these megakaryocytic abnormalities or some of them were found in the marrow smears splenectomy should not be advised Further experience has however not confirmed these suggestions Although cases do exist in which the megakaryocytes show degenerative changes or have failed to form cytoplasmic granules most patients with primary thrombocytopenic purpura have *normal* megakaryocytes (e g see Schwarz 1948) The really difficult differential diagnosis is from the aplastic type anæmias who still have a fairly active marrow megakaryocytes may be notably few in the bone marrow of such patients The only reasonable precaution that can be recommended at present is that if megakaryocytes are *not* found in the sternal marrow smears splenectomy should be deferred for further marrow examinations from other sites perhaps and the patient watched for a while to see if the diagnosis becomes clearer

For secondary thrombocytopenic purpura splenectomy is contraindicated and blood transfusion is the treatment most of the patients recover though some may need transfusions for months Splenectomy has been considered recently for some of the cases secondary to other blood diseases the question is discussed in the section on hypersplenism (p 214)

A (3) **Hypoprothrombinæmia** Congenital hypoprothrombinæmias sometimes running in families have been detected some were reported by Quick (1947b) The affected persons seem to suffer little disability but may sometimes bleed unduly after tooth extraction

The treatment of hæmorrhagic disease of the new born and of hæmorrhage in salicylate poisoning with transfusion of fresh blood and parenteral vitamin K is now well established

Plasma prothrombin is diminished in parenchymatous liver disease It is characteristic that neither oral nor parenteral administration of vitamin K produces the dramatic rise in plasma prothrombin usually seen in obstructive jaundice

A (4) **Parahæmophilia** This condition due to absence of the plasma prothrombin accelerator that Owren calls factor V is very

Blood transfusion has always been the stand by of treatment The anti hæmophilic activity of the plasma was localised to a globulin fraction I and actual anti hæmophilic globulin was prepared in the U S A in 1946 its action however has been somewhat uncertain Alexander and Landwehr (1948) showed that the activity of the anti hæmophilic plasma factor deteriorates rapidly when stored under normal conditions and they prepared special fractions that were *frozen and dried within half an hour* of the blood being drawn from the donor These fractions kept well and an intravenous infusion of 150 ml of the reconstituted plasma would keep the blood coagulation time of a hæmophilic patient normal for 24 hours and near normal for 48 hours This preparation clearly has possibilities if its activity is confirmed and it can be made on a large scale, but this has not yet been done Alexander and Landwehr s observations however emphasise that for the successful control of hæmophilic hæmorrhage *fresh blood* i e blood given within ½ hour of withdrawal from the donor must be used, and transfusions must be repeated daily, or at least every second day until hæmorrhage ceases

By following this principle it is now practicable to undertake dental extraction in the hæmophilic patient without undue risk full details are given by Matheson (1949) Schiller *et al* (1948) have shown how even a major operation like a laminectomy can be successfully performed The risks to which the hæmophiliac is exposed remain severe internal hæmorrhages especially into the gastro intestinal tract are difficult to control, hæmarthroses may cause severe crippling and hæmorrhages into the tissues under the tongue and other vital areas may prove rapidly fatal Nevertheless it is remarkable how many patients survive through adult life and the newer tests have shown up many mild cases

Hæmophilia has always been thought of as limited to the male sex The theory of sex linked inheritance however postulated that if a male hæmophiliac married a female carrier female children of the marriage could be either hæmophilia carriers or true hæmophiliacs But no true hæmophilic female had been recorded Israels Lempert and Gilbertson (1951) have now filled this gap by describing a family of two daughters of a marriage of the required type one is known to be a hæmophilia carrier and the other has been shown to have true hæmophilia The methods used to establish the diagnosis were based on the findings described in this chapter and show the many methods now available for confirming a diagnosis of hæmophilia and eliminating hæmophilia like diseases

A (2) Thrombocytopenic purpura The clinical picture of the *primary* form is well known and the treatment recommended is splenectomy But splenectomy is not always successful there are some patients whose platelet count does not rise as expected after

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Blood transfusion has always been the stand by of treatment The anti hæmophilic activity of the plasma was localised to a globulin fraction I" and actual anti hæmophilic globulin was prepared in the U S A in 1946 its action however has been somewhat uncertain Alexander and Landwehr (1948) showed that the activity of the anti hæmophilic plasma factor deteriorates rapidly when stored under *normal conditions*, and they prepared special fractions that were *frozen* and dried within half an hour of the blood being drawn from the donor These fractions kept well and an intravenous infusion of 150 ml of the reconstituted plasma would keep the blood coagulation *time* of a hæmophilic patient normal for 24 hours, and near normal for 48 hours This preparation clearly has possibilities if its activity is confirmed and it can be made on a large scale, but this has not yet been done Alexander and Landwehr s observations however emphasise that for the successful control of hæmophilic hæmorrhage *fresh blood* i e blood given within ½ hour of withdrawal from the donor must be used and transfusions must be repeated daily or at least every second day until hæmorrhage ceases

By following this principle it is now practicable to undertake dental extraction in the hæmophilic patient without undue risk full details are given by Matheson (1949) Schiller *et al* (1948) have shown how even a major operation like a laminectomy can be successfully performed The risks to which the hæmophiliac is exposed remain severe internal hæmorrhages especially into the gastro intestinal tract, are difficult to control, hæmarthroses may cause severe crippling and hæmorrhages into the tissues under the tongue and other vital areas may prove rapidly fatal Nevertheless it is remarkable how many patients survive through adult life and the newer tests have shown up many mild cases

Hæmophilia has always been thought of as limited to the male sex The theory of sex linked inheritance however postulated that if a male hæmophiliac married a female carrier female children of the marriage could be either hæmophilia carriers or true hæmophiliacs But no true hæmophilic female had been recorded Israels, Lempert and Gilbertson (1951) have now filled this gap by describing a family of two daughters of a marriage of the required type one is known to be a hæmophilia carrier and the other has been shown to have true hæmophilia The methods used to establish the diagnosis were based on the findings described in this chapter and show the many methods now available for confirming a diagnosis of hæmophilia and eliminating hæmophilia like diseases

A (2) Thrombocytopenic purpura The clinical picture of the *primary* form is well known and the treatment recommended is splenectomy But splenectomy is not always successful there are some patients whose platelet count does not rise as expected after

splenectomy while hæmorrhages may continue unchecked The proportion of these resistant cases that are truly primary is probably not more than ten per cent but they are disconcerting and efforts have been made to detect them before splenectomy With this object in view the megakaryocytes of the bone marrow have been critically examined Dameshek and Miller described the occurrence of peculiar megakaryocytes with a basophilic non granular cytoplasm that they called lymphoid forms others have placed emphasis on the occurrence of early forms of megakaryocytes—normally very unusual in bone marrow smears—or in the presence of mature cells without the usual granule formation in the cytoplasm It has been suggested that unless these megakaryocytic abnormalities or some of them were found in the marrow smears, splenectomy should not be advised Further experience has however not confirmed these suggestions Although cases do exist in which the megakaryocytes show degenerative changes or have failed to form cytoplasmic granules most patients with primary thrombocytopenic purpura have *normal* megakaryocytes (e g see Schwarz 1948) The really difficult differential diagnosis is from the aplastic type anæmias who still have a fairly active marrow megakaryocytes may be notably few in the bone marrow of such patients The only reasonable precaution that can be recommended at present is that if megakaryocytes are *not* found in the sternal marrow smears splenectomy should be deferred for further marrow examinations from other sites perhaps and the patient watched for a while to see if the diagnosis becomes clearer

For secondary thrombocytopenic purpura splenectomy is contraindicated and blood transfusion is the treatment most of the patients recover though some may need transfusions for months Splenectomy has been considered recently for some of the cases secondary to other blood diseases the question is discussed in the section on hypersplenism (p 214)

A (3) **Hypoprothrombinæmia** Congenital hypoprothrombinæmias sometimes running in families have been detected some were reported by Quick (1947b) The affected persons seem to suffer little disability but may sometimes bleed unduly after tooth extraction

The treatment of hæmorrhagic disease of the new born and of hæmorrhage in salicylate poisoning with transfusion of fresh blood and parenteral vitamin K is now well established

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A (4) **Parahæmophilia** This condition due to absence of the plasma prothrombin accelerator that Owren calls factor V is very

rare but is likely to be confused with hæmophilia Owren (1947) described one case a female and a very few others have been mentioned in the literature It is congenital but apparently not hereditary Transfusion of reasonably fresh blood promptly stops the hæmorrhage

A (5) **Fibrinogenopenia** This exists as (1) a congenital complete absence of fibrinogen, in which the blood is completely incoagulable The bleeding time may be prolonged and the platelet count reduced to about half normal, and (2) a ' constitutional ' form in which there is only about 1/10th the normal amount of fibrinogen in the blood —normal figures are 0 22 to 0 36 gram per 100 ml The clotting time is several hours the bleeding time may be prolonged and the platelets are usually normal These cases can be distinguished from hæmophilia by showing that fibrinogen is absent or greatly reduced in the plasma Quick has described two tests for this —(1) half saturation with sodium chloride or quarter saturation with ammonium sulphate will precipitate the fibrinogen, (2) fibrinogen coagulates at 56°C, so if the plasma is heated to 60°C and remains clear there is no fibrinogen

A (6) **Circulating anticoagulants** Patients with prolonged coagulation time associated with a circulating anticoagulant in the blood have been described The patient s plasma will prolong the coagulation time of normal plasma Nearly all the patients have been women but Dieter *et al* (1949) described a male patient No question of heredity has arisen They are, of course likely to be confused with hæmophiliacs Allen *et al* (1949) have suggested that the anticoagulant is ' heparinoid ' in nature and have therefore used injections of toluidine blue or protamine sulphate for treatment

Allen and Jacobson had previously detected similar anticoagulants in the blood of dogs exposed to a single dose of 450r of X rays applied to the whole body These dogs had low platelets together with prolonged blood coagulation times the hæmorrhages did not respond to blood transfusion but did to toluidine blue It is possible that hæmorrhages occurring after exposure to atomic explosions may be similar

Group B (1) Hereditary Hæmorrhagic Telangiectasia This disease often causes intractable recurrent epistaxis and is detected by the characteristic lesions that are seen not only on the nasal mucosa but also on the tip of the tongue under the nail beds and elsewhere It is peculiarly resistant to treatment Cochrane and Leslie (1950) have suggested the use of small doses of contact X rays for treatment

B (2) **Schonlein Henoch syndrome** This is the commonest form of non thrombocytopenic purpura and presents the clinical picture of a rash together with gastro intestinal symptoms caused by hæmorrhages into the wall of the gut or painful swellings round joints but not hæmarthroses Gairdner (1948) has described the rash in some

detail and considers it to be specific for the syndrome He points out that at first it is a small irritant urticarial rash mainly on the extensor surfaces of the upper and lower limbs in a few hours pink raised maculo papules appear and then the hæmorrhagic element changes the colour to red then dusky purple and finally fades to brown The typical histological picture is described as acute aseptic perivascular inflammatory reaction in the corium with some tissue eosinophilia Although this syndrome is often put down to increased capillary fragility as judged by positive pressure tests of the Gothlin type Gairdner like others found the fragility usually normal Nor was he able to find the capillary abnormalities described by Macfarlane Gairdner argues persuasively in favour of the idea that this form of purpura is closely allied to rheumatic fever periarteritis nodosa and acute nephritis He suggests that an antigen antibody reaction is the cause but admits that the evidence is poor At all events it does seem likely that this form of purpura can be grouped with the so called collagen diseases

The treatment of Schonlein Henoch purpura is disappointing Rutin has in the long run not proved of any value at all Vitamin P preparations have been equally disappointing and it is now doubtful whether in fact citrin and similar substances have a vitamin like action or whether any clinical deficiency of such substances occurs (see *Lancet* 1950) If the relation to collagen diseases is sustained cortisone may prove effective Spontaneous recovery with bed rest is so common in this purpura that assessment of the value of any form of treatment is difficult Recurrences are frequent in some patients and splenectomy has not prevented them

B (3) Pseudohæmophilia This name is best reserved for a group of patients whose clinical picture in some aspects resembles true hæmophilia but whose blood clotting is quite normal When there is a family history females are affected as often as males They usually come for advice because of severe bleeding after tooth extraction or the formation of a large and persistent hæmatoma after trauma On the other hand operations involving cutting have often been performed without incident They are fortunately rare because they are often more difficult to deal with than patients with true hæmophilia The history is usually that a tooth has been removed at first all appeared well but after three or four days hæmorrhage from the socket has begun and persists On examination a large blood clot is found with firm fibrin As soon as this is cleared away bleeding begins again All tests for blood coagulation are normal The only treatment is thorough packing and the use of local styptics Blood transfusion may be needed to redress the fall in hæmoglobin and it may well be four to six weeks before the hæmorrhage is finally controlled Local

abnormalities of blood vessels are thought to be the cause and Macfarlane's patients whose capillaries did not contract on injury may well be put in this group

B (4) and (5) The purpuras in nutritional and infectious diseases are self explanatory Ackroyd (1949) has surveyed the incidence of purpura in infectious diseases and points out that the platelet count is occasionally very low for a few days

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LEUKÆMIA

Leukæmia is roughly classified by most physicians into two forms chronic for which X ray treatment is given and life may be prolonged *for two or three years* and acute *for which no treatment* is any use and the patient dies in two or three months Physicians realise that hæmatologists have learned arguments about the nature of the cells found in the blood and bone marrow especially in the acute forms but the results of these deliberations make no difference to what happens to the patient In the last few years however several new ways of treating leukæmias acute and chronic have been tried and though the results have not always been good they have been sufficiently encouraging to make *further research worthwhile* so the patient

should at least be given the benefit of a trial Now advances in treatment make refinement of diagnosis more important and leukæmia is no exception to this rule The previous sterile observations on the cells of blood and bone marrow have now a therapeutic application and early diagnosis has become a very important matter for the patient Therefore together with the discussion of these newer methods of treatment the diagnosis of leukæmia must also be briefly mentioned

The diagnosis of leukæmia depends on finding in the blood *and* the bone marrow the typical hæmatological changes Of the two the bone marrow is the more important If a patient has a peripheral blood picture suggestive of leukæmia but the bone marrow does not show leukæmic changes the diagnosis of leukæmia cannot be sustained and the clinician must consider alternative diagnoses More frequently the blood picture is uninformative though leukæmia is suspected on clinical grounds while bone marrow examination may confirm the diagnosis by showing a leukæmic picture This is not the place to discuss the details of hæmatological diagnosis and those interested are referred to the Atlas of Bone Marrow Pathology (Israels 1948) It is enough to say that the diagnosis of the type of chronic leukæmia should never be in doubt It can be myeloid (granulocytic) lymphatic or rarely monocytic In the acute and sub acute leukæmias the differentiation of the type may be difficult especially if the patient is seen late but the attempt should be made to find out whether it is myeloblastic myelocytic lymphatic monocytic or an undifferentiated stem cell type As will be seen later the prognosis with treatment depends to a certain extent on the type for example cortisone and ACTH are the best treatment for acute lymphatic leukæmias

Chronic Leukæmias

Diagnosis The diagnosis is easy when the patient presents with an enlarged spleen with or without enlarged lymph glands and the blood picture shows anæmia gross leucocytosis and a differential count characteristic of myeloid or lymphatic leukæmia Most patients present in this way but there are some difficulties Some cases of chronic myeloid leukæmia have little anæmia a grossly enlarged spleen and no leucocytosis (i e not more than 10 000 white cells p c mm) but there will be 10–20 per cent of immature granulocytes an occasional myeloblast and some normoblasts The bone marrow shows an excess of granulocytes but few myeloblasts The differential diagnosis here is from myelosclerosis and it is advisable to treat the anæmia and avoid any of the specific leukæmic treatments until the diagnosis is clearer Some patients with chronic lymphatic leukæmia

have enlarged lymph glands no anæmia no leucocytosis, but characteristic bone marrow changes In these patients too although the diagnosis is clear the special treatments should not be given until increasing anæmia or increasing enlargement of lymphatic tissue (including the spleen) make it necessary Such patients often survive for years with only simple anti anæmic treatment

Treatment X ray treatment has been the stand by for many years and is still widely used Consideration of large series of cases has shown that the *average* length of survival is not greatly prolonged it is two to three years However a minority of patients respond very well and have lived for longer periods 5–15 years Great comfort is obtained for the patient by the reduction in size of the spleen and lymph glands It is doubtful whether the newer forms of treatment have improved on these figures but they are often much more convenient to apply and may be less disturbing for the patient

Urethane was introduced in 1946 by Paterson and Haddow It has the advantage that it can be given by mouth but the disadvantage that it often induces unpleasant nausea It is cheap and plentiful and has been extensively used especially on the Continent the dose is 3–6 grams daily These trials have shown that it is only really useful in chronic myeloid leukæmia and even in this the more active nitrogen mustard preparations are now generally preferred

Nitrogen Mustards This name is now applied to two substances methyl *bis* (β chloroethyl) amine hydrochloride and *tris* (β chloroethyl) amine hydrochloride known shortly as the 'bis' and 'tris' forms Experience with workers who prepared these substances showed that they often suffered from leucopenia and this suggested their use in leukæmia Investigation has shown that they have a selective action on rapidly growing cells In adult man the bone marrow and the lymph nodes are the most important sites of active cell division and in leukæmias this activity is greatly increased The drugs have been tried out in leukæmias in Hodgkin s disease and other reticuloses in polycythæmia vera and some neoplastic diseases Experience has *shown that their practical use in man is limited* to the chronic leukæmias Hodgkin s disease and polycythæmia vera

Special precautions have to be taken about their administration This is not only because they are powerful vesicants but because the substance that causes the therapeutic effect is a hydrolysis product from the actual mustard material and this reactive hydrolysate is soon further converted to a relatively inactive product (Wilkinson and Fletcher 1947) Nitrogen mustards are therefore dispensed in solid or semi solid form and the solution is prepared immediately before use The solution has to be given intravenously To prevent local thromboses and damage to the vein a fast running saline drip is set

up and the nitrogen mustard solution slowly added to the running stream usually by injecting it from a syringe through the rubber tube of the drip After the mustard solution has all been given about 100 ml of saline are allowed to run through

The usual dose is 0 1–0 2 mg per kg with a maximum of 6 mg The doses are given at first on alternate days, but shortly at longer intervals Initial treatment *must* be controlled by daily white cell counts and bi weekly full blood counts As soon as the daily white cell count shows a significant fall treatment is stopped until the count levels out again In most patients with chronic myeloid or lymphatic leukæmia it is sufficient to reduce the total white cell count to about 30 000 p c mm If the treatment is really effective the size of the spleen and lymph glands should be reduced and the anæmia if present should improve After the initial course, no more treatment need be given until an enlarging spleen increasing white cell count and falling hæmoglobin show it to be necessary Then doses can be given at weekly intervals and it is safe to give the dose in an out patient clinic

Nitrogen mustard treatment has two disadvantages (1) the necessity for a special type of intravenous administration limits its use to the special clinic particularly for continued out patient use (2) in about half the patients the drug induces a nausea and vomiting of central origin a few hours after the dose This can sometimes be controlled by antihistamine drugs but in a few patients the reaction has been so severe that treatment has had to be given up In order to avoid the difficulty of intravenous administration some chloroethylamine compounds that can be given orally have been tried and one of them β-naphthyldi 2 chloroethylamine has had some success (e g Matthews 1950) It is noticeably less active than the intravenous forms but experience with it at Manchester suggests that it is useful for controlling mild cases of chronic myeloid leukæmia and Hodgkin s disease The dose is 100 mg daily for the first two weeks further doses being regulated by the clinical and hæmatological progress

Four years experience with nitrogen mustards has shown that on the whole it gives the same sort of result as X ray treatment About one quarter of the patients respond satisfactorily in every way and about one quarter respond poorly from the first In about half the cases a good response is obtained for a period of 18 months to two years after onset then resistance to the effect of the drug sets in the spleen no longer shrinks so well the anæmia becomes more stubborn and supporting blood transfusions become necessary This is the beginning of the end though it is impossible to give an accurate prognosis even at this stage because unexpected remissions can still occur

At the time of writing nitrogen mustard treatment is probably the one most used for chronic leukæmias but it would be idle to pretend

that it offers much improvement over X rays and it will certainly be replaced with alacrity if something better is developed

Radio phosphorus The radio active phosphorus isotope P^{3} is selectively taken up by lymphocytes and by the cells of bone marrow liver, and spleen Its application to the treatment of chronic leukæmias was therefore begun early J H Lawrence and his associates in California have had most experience and they have published results obtained with 129 cases of chronic myeloid leukæmia (Lawrence *et al* 1948) and 100 cases of chronic lymphatic leukæmia (Lawrence *et al* 1949) The results are very similar to those obtained with X rays and nitrogen mustards Radiophosphorus has the advantage that it can be given orally or intravenously, and since it is a β ray and not a γ ray emitter it is relatively safe to handle There are, unfortunately several disadvantages (1) since its half life is 14 3 days the treatment centre must be near or in rapid communication with the production centre (2) the dose varies greatly from patient to patient and it has not been found practicable to adjust it on a body weight basis this means that close control with frequent blood counts is necessary, (3) doubts about the long term effect of even relatively inactive radio active materials have led to a general recommendation that they should not be used for the treatment of patients in the reproductive period of life or those whose expectation of life exceeds five years

Splenectomy This operation used to be done for chronic leukæmia but was soon abandoned because of the very poor results It has recently been recommended again for patients whose leukæmia appears controlled but who have a resistant anæmia (see Hypersplenism p 214)

Acute Leukæmia

Diagnosis The diagnosis of acute leukæmia is too often missed or not made until the disease is at a late stage and all hope of control has gone The practitioner thinks of the acute leukæmic patient as presenting with pyrexia severe anæmia hæmorrhages enlarged spleen and lymph glands and a rapid downward course The blood count shows anæmia often gross a high white cell count and most of the white cells are primitive types This classical picture is of course quite correct but at least half the cases present differently and it is among this less typical more insidious group that remissions have most often been induced by treatment The patients in this less characteristic group come to notice for two reasons (1) They have anæmia for which there appears to be no reason There is no enlarged spleen lymph glands are unaffected and a search reveals some petechiae but no other hæmorrhages The blood count shows anæmia that is frequently macrocytic and therefore liable to be confused with pernicious

anæmia The white cell count is often normal or sub normal The differential count is also normal or there may be a few primitive cells which are often reported as lymphocytes The platelets are usually low The diagnosis in such patients turns on the bone marrow which is found to contain a majority of primitive leucoblasts (2) They have a hæmorrhagic episode—severe and prolonged epistaxis hæmaturia hæmatemesis menorrhagia—or an enlarged lymph gland is noted Swollen often bleeding gums may send them to the dentist Here again examination of the peripheral blood may yield the diagnosis immediately but in many patients only bone marrow examination gives a convincing answer The lesson to be learnt here is that unless the cause of the anæmia is quite clear from the beginning no patient with anæmia has been properly investigated until a marrow examination has been made

Treatment *Blood Transfusion* This has always been the first line of treatment in acute leukæmia and there are several records in the literature of remissions that have followed blood transfusion most of them in children In 1947 Bessis and Bernard applied to acute leukæmia the technique of exchange transfusion which had been successfully used in erythroblastosis of infants It was in adults a formidable procedure involving exsanguination of the patient and transfusion of 14 or 15 pints of compatible blood Good results were claimed at first but subsequent experience has shown that even in those patients whose blood and bone marrow pictures became almost normal after treatment relapse followed in about three months (see Croizat *et al* 1948) The technique is now abandoned It has however served to remind us that blood transfusion in acute leukæmia may not be an entirely neutral procedure and this has to be taken into account when trying to assess the results of other treatments

Folic acid antagonists In animal experiments folic acid deficiency is notable more for the leucopenia than for the anæmia it causes It was therefore surmised that folic acid antagonists—closely related substances that block the growth promoting activities of folic acid *in vitro*—might reduce the growth of primitive leucocytes in acute leukæmia Several such substances were known and they were tried out on transmissible mouse leukæmia which has some features similar to those of human acute leukæmia These tests indicated that aminopterin and amethopterin were the most active substances and in man aminopterin proved the most effective

Aminopterin is a very toxic drug It is given orally or intramuscularly The oral dose is 1 mg daily The intramuscular dose is two successive doses of 1 mg Control by daily white cell counts and bi weekly full blood counts is essential because it is easy to induce a dangerous depression of all marrow activity In 1948 Farber and

his colleagues reported that they had induced temporary remissions of acute leukæmia in children A later report by Sacks and co workers (1950) is typical Fourteen patients with various forms of acute leukæmia were treated and temporary complete remissions were induced in two an adult with acute myeloblastic leukæmia and an infant with acute lymphatic leukæmia By complete temporary remission they meant that peripheral blood and bone marrow patterns were normal and there was clinical recovery as well The adult relapsed after 81 days and the infant after three months, both died Partial temporary remissions occurred in three other patients who died subsequently Innes (1950) has reported longer remissions in children with acute lymphatic leukæmias induced by giving 0 5 to 1 0 mg orally daily and maintaining the dose in spite of side effects and grave leucopenia Even so relapse occurred while treatment was being given in some patients

Personal and published experience is similar Some longer remissions have been seen and some patients have responded to second courses of treatment but the remissions have never been more than temporary In perhaps two thirds of the patients there is no useful effect

Adrenocorticotrophic hormone (ACTH) and cortisone One of the earliest described effects of ACTH was its ability to reduce lymphoid tissue and cause dissolution of lymphocytes It was not unexpected therefore that ACTH and cortisone would have some effect in lymphatic leukæmia A report by Dameshek and others (1950) showed that remissions affecting peripheral blood and bone marrow were induced in four out of five children with lymphatic leukæmia of the leucopenic type Coincident reticulocytosis and increase of platelets suggested that the hormone actually stimulated the remaining normal marrow cells an effect not seen with any other substance used for the treatment of leukæmia The dose of ACTH used was equivalent to 80 mg daily of Armour standard for 14 days and then 40 mg twice weekly for maintenance Damashek stated that such remissions might be only temporary and this warning has unfortunately been justified by subsequent experience Stickney *et al* (1950) used larger doses 200 mg daily of ACTH and 200–300 mg of cortisone daily for adults with 50–75 per cent of this dose for children Of 12 patients with acute leukæmia treated with cortisone two had proper complete remissions one out of six patients treated with ACTH remitted A disturbing feature was that when they relapsed they did not respond to second courses of treatment

Subsequent experience has on the whole confirmed these early reports So far ACTH and cortisone appear to be of value only in acute lymphatic and possibly stem cell leukæmias (In chronic

lymphatic leukæmia Stickney found that although the size of the spleen and lymph glands was reduced the blood and marrow pictures remained unchanged) The remissions when induced are temporary Now that ACTH and particularly cortisone are becoming more plentiful further reports are likely to appear and may enable their value to be assessed more precisely

It must be emphasised that in addition to these treatments directed at the leukæmic process treatment of the anæmia is equally important Patients having aminopterin all need blood transfusion sooner or later owing to the depressant effect of the drug on normal erythropoiesis Patients having ACTH or cortisone need to be transfused if anæmic because complications due primarily to the anæmia may prove fatal before the specific drugs have time to act In remission an iron deficiency type of anæmia may develop especially if there has been much hæmorrhage it should be treated appropriately with iron

A great deal of effort is now being put into the treatment of acute leukæmia because the condition seems to be increasing in incidence and so many of the patients are young So far we have hardly done more than control some cases but the very fact that it has proved possible to reverse the clinical and hæmatological picture even in a few patients suggests that the quest for a successful treatment is not hopeless

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BLOOD GROUPS AND THE RH FACTOR

A certain order has appeared out of the temporary confusion of the blood group scene Apart from minor varieties seven systems of

blood groups have now been identified Each group is immunologically distinct and genetically unrelated to the others Within each group there are a number of genetically related variants—Mendelian allelomorphs The seven systems are as follows —

(1) ABO, the original blood groups recognised antigens A_1 A_2 B, and O (O is now recognised as a definite antigen and not just absence of A and B anti O antibody though rare has been reported)
(2) Rh recognised antigens C C^w c D d E e
(3) MNS antigens M N, and S (S is a newly discovered factor that has been found to be genetically related to Landsteiner s original M and N)
(4) P with one antigen
(5) Lewis with two antigens
(6) ' Kell with two antigens
(7) ' Lutheran " with one antigen

There are thus 20 antigens in the seven systems and this means that there are identifiable to day some 46 000 possible phenotypes (identifiable antigen compositions of the red cell) and some 630 000 possible genotypes—inherited gene patterns It is indeed fortunate that only the ABO and Rh systems are of clinical importance and only these groups need to be ascertained in routine blood transfusion work in Europe A further saving of effort is possible because only D among the Rh antigens is at all potent in the production of antibodies So for practical cross matching purposes only A B O and D have to be tested for The many other antigens have however some clinical and medico legal importance In cases of disputed parentage the presence of so many possibilities has immensely increased the chance that a wrongfully accused father will be able to prove his innocence provided the courts will order—and act upon—blood group tests on father mother and child The work is difficult and can only be properly carried out in a few places

Clinically these groups are important in the aetiology of erythroblastosis in infants and in the aetiology of reactions during and failure of effect of blood transfusions in persons who have received multiple transfusions It must be remembered that the only naturally occurring antibodies in man are anti A anti B and a weak anti P that occurs only as a cold agglutinin All other antibodies are produced as a reaction to the presence of antigens in the blood of a person who is naturally without them the antigens are there either because the patient has received them in a blood transfusion or because a mother receives them from her fœtus Fortunately again most of the possible antigens do not stimulate the formation of antibodies in sufficient amounts under

usual conditions to do any damage Apart from A and B the only effective antigen is D of the Rh system and even the effects of D are limited Diamond and Allen (1949) point out that about 50 per cent of D negative persons are immunised by a single transfusion of D positive blood *Ninety five per cent* of D negative women with D positive husbands and a D positive fœtus *never* develop anti D antibodies and so their infants will not have erythroblastosis Again of all persons who do become immunised to Rh antigens 95 per cent have anti D antibodies a few have anti c or anti E or both only an *extremely small fraction have others*

Erythroblastosis in infants It is now accepted that erythroblastosis in its various forms occurs because the fœtus has a different blood group from its mother The fœtal red cells have stimulated in the mother s blood the production of antibodies of sufficient strength to cause agglutination or actual hæmolysis of the fœtal red cells when the antibodies in their turn pass across the placenta from mother to fœtus It is the Rh antibodies that are dangerous and as we have seen in 95 per cent of cases it is the anti D antibody that is responsible If then the father is D positive and the mother D negative there is a chance that the child will have erythroblastosis the chances will be much increased if the mother has, for any reason had a previous transfusion of Rh positive blood or if previous children have been affected If incompatibility exists it should be possible to detect the anti D antibodies in the mother s blood Mollison (1948) recommends that two examinations should be made during pregnancy the first early in pregnancy and the second six weeks before the expected delivery date The first examination will show up any sensitivity acquired before pregnancy the second will show sensitivity arising from the pregnancy under way

However it was at first found that sometimes anti D antibodies could not be detected in the mother s serum when all the circumstances indicated their presence Investigation of this problem has led to the discovery that anti D antibodies exist in more than one form The usual technique for detecting them is to expose D positive red cells *suspended in saline to their action and observe the resulting agglutina* tion When this happens saline agglutinins are said to be present Research showed that in addition there are anti D antibodies which in saline only coat the red cells without agglutinating them but in a 20 per cent albumin solution agglutination takes place as usual— these agglutinins are called albumin agglutinins Diamond found that if repeated doses of Rh positive blood are injected into healthy Rh negative persons the saline antibodies appear first and are then replaced by the albumin antibodies he regards the latter therefore as hyperimmune Once the albumin antibodies have acted on the

red cells, the cells cannot be agglutinated by the most active saline antibodies The albumin antibodies are therefore said to have blocked *the agglutination of the coated red cells* Recently Hill Haberman and Guy (1949) have described yet a third variant of antibody which coats red cells but does not block their agglutination This antibody is inactive in saline

A way out of all these difficulties was found by Coombs Mourant and Race (1945) who showed that an anti human globulin serum prepared by injecting human serum globulin into rabbits will agglutinate coated red cells, whatever the type of antibody responsible *This* Coombs test " as it is called is most valuable for detecting red cells that have been affected by anti Rh antibodies and it has other applications as well It can show up red cells that have absorbed antibodies in acquired hæmolytic anæmias and in paroxysmal cold hæmoglobinuria Details of techniques are given in the M R C memorandum quoted in the reference list

Prevention of erythroblastosis Haldane has said that this hæmolytic syndrome is responsible for more deaths than any other inherited disease Induction of labour four to six weeks before term early post natal transfusion with Rh negative blood and early exchange transfusion have done a lot to minimise the effects of erythroblastosis and transfusion has restored some affected infants to perfect health But it is known that much damage especially to the central nervous system occurs before birth and therefore if a way of neutralising the Rh antibodies in the mother could be found this would be the ideal mode of treatment It is with this object that attempts have been made to prepare the Rh hapten The hapten is that part of the immune body which together with complement combines with the immune antibody and neutralises its properties Extraction of Rh antigen and hapten from red cell stroma was reported as early as 1946 its preparation and successful clinical trial was reported by Carter and her co workers in 1947 and 1949 The substance obtained was claimed to reduce the titre of Rh antibodies in the mother s serum and to neutralise the antibodies present in the blood of affected infants so that they recovered with at most a single transfusion of 100 ml of blood The importance of this claim if confirmed can hardly be exaggerated Unfortunately it has not so far been confirmed and a typical adverse report is that of Wolf *et al* (1950) who prepared Carter s hapten and tried it in 22 pregnancies *The occasional good* result was no more than could be expected from the natural variability of the disease and though they agree that the material probably is hapten in character its potency is very low No Rh sensitised woman *they say should be encouraged to conceive in the hope* that hapten therapy will alter the prognosis for the child

Chown (1949) has pointed out that the common practice of using the father s blood to give to the mother if both have the same ABO and D phenotype is dangerous and liable to produce erythroblastosis when completely unexpected A mother and father were both group O and D positive After the birth of their second child, mother received a transfusion from father The third child had erythroblastosis of the general œdema type and died Research eventually incriminated the Kell system It is clear that if the father has one of these less common factors and mother has not the baby may inherit it and then transfusion from father is the one certain way to ensure that the mother will become sensitised to the unusual factor

The part played by incompatibility to the less common blood group systems is not yet worked out Patients who have developed anti bodies to as many as nine factors have been described and it is quite possible that future research may be able to link some obscure anæmias, perhaps from the rag bag of unexplained hæmolytic anæmias with these multiple sensitisations to blood group antigens Blood grouping technique especially the detection of sensitisation is being rapidly improved and may help to provide the missing clues

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TRANSFUSION SUBSTITUTES

Ever since Bayliss introduced gum acacia solution in the first world war efforts have been made to find an artificial fluid that could be infused to restore the volume of the circulating blood Such fluids are valuable for the treatment of shock accidental hæmorrhage and in fact for any condition in which the circulating blood volume is suddenly reduced and the patient needs tiding over until the processes of natural recovery can come into play The development of blood banks in the past decade and the fact that during the second world war the banks had often much unused time expired blood available

red cells, the cells cannot be agglutinated by the most active saline antibodies The albumin antibodies are therefore said to have "blocked" the agglutination of the coated red cells Recently Hill Haberman and Guy (1949) have described yet a third variant of antibody which coats red cells but does not block their agglutination This antibody is inactive in saline

A way out of all these difficulties was found by Coombs Mourant and Race (1945) who showed that an anti human globulin serum prepared by injecting human serum globulin into rabbits will agglutinate coated red cells, whatever the type of antibody responsible This 'Coombs test' as it is called is most valuable for detecting red cells that have been affected by anti Rh antibodies and it has other applications as well It can show up red cells that have absorbed antibodies in acquired hæmolytic anæmias and in paroxysmal cold hæmoglobinuria Details of techniques are given in the M R C memorandum quoted in the reference list

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on hydrolysis into fractions of lower molecular weight By interrupting the hydrolysis at a suitable point it is possible to get a dextran solution with most of the molecules in the desirable range from about 70 000 to 100 000

By fractionation it has proved practicable to obtain a reasonably homogeneous preparation containing only a small proportion of molecules that are too small—and are therefore rapidly excreted—or too large and responsible for toxic reactions particularly in the kidney A suitable dextran solution was prepared by Swedish workers and first tested out by Gronwall and Ingleman in 1944 After animal experiments it was distributed to certain clinics for testing in shock due to injury and operation The results were very encouraging and in 1947 dextran was produced in Sweden on a commercial scale in the form of a six per cent solution In 1949 Thorsen was able to state that 107 Swedish hospitals had given 25 000 transfusions with dextran There had been some unpleasant reactions 0 3 per cent had urticaria and 0 4 per cent pyrexial reactions This compares well with the reaction rate of any transfusion fluid including whole blood The results in shock in burns and in acute anæmia were so satisfactory that it had replaced plasma for these purposes It has also been used for giving temporary relief in hypoproteinæmic conditions such as nephrosis

Interest in dextran has been stimulated by the preparation in this country of a product that is free from protein and has a mean molecular weight of 75 000 ± 10 per cent This preparation was reported by Bull *et al* (1949) to be non toxic non pyrogenic and produced no antigens They tried it out on 29 patients undergoing major operations and reported results as very satisfactory There are however two undesirable properties The first is that dextran infusions cause an increased sedimentation rate of red cells and at concentrations of 0 5 g per 100 ml can cause actual rouleaux formation The effect has been shown to be due to larger molecules of weight 40 000 upwards In practice such concentrations are not reached but the presence of dextran in the patient s plasma may cause difficulty with direct cross matching tests for blood grouping owing to rouleaux formation in the donor s blood Blood for cross matching is therefore best taken *before* dextran is given

The second point concerns the fate of dextran With present preparations about 25–30 per cent of dextran is excreted in the urine during the first 24 hours The fate of the remaining 75 per cent is not clear Bull *et al* using a serological method were able to detect dextran in the tissues of rabbits 56 days after infusion and some excretion in the urine went on for 12 days Engstrand and Åberg (1950) have produced evidence that suggests that dextran is excreted

allowed human plasma to be prepared in large quantities This plasma was dried from the frozen state and kept ready for reconstitution when required But plasma has its disadvantages many countries have not got blood transfusion services there is to day a much smaller surplus of blood available for plasma preparation, the risk of transmitting homologous serum jaundice has made plasma unpopular reconstituted plasma often causes unpleasant reactions and plasma is *unsuitable* for tropical climates For all these reasons there has grown up a practice of using whole blood in circumstances when plasma *would be enough* If a really reliable artificial fluid were available it could be used instead and so spare blood for those patients who *must have it* It could be held available for instant use and no incompatibility difficulties would arise

The requirements for a suitable artificial transfusion fluid are numerous and have been well set out by Bull *et al* (1949) —

(1) The colloid solutes should be retained in the circulation until their place can be taken by natural proteins This implies that the colloids should not pass readily into the tissue fluids nor be rapidly excreted, so that a molecular weight of at least 70 000 is necessary Also it should not be rapidly metabolised
(2) Its osmotic pressure and viscosity must be similar to those of plasma
(3) Its composition must be reasonably constant
(4) It should be stable when stored and preferably should not need special storage conditions (like refrigeration)
(5) It must not be locally or generally toxic
(6) It must not induce fever
(7) It must not induce sensitisation
(8) It must not be stored for long periods in the tissues
(9) It must not be diuretic because it contains large amounts of solutes of low molecular weight
(10) Easy sterilisation and reasonable cost of large scale production are desirable

This is a very comprehensive programme Many substances have been tried—pectin gelatin bovine albumin bovine plasma isinglass methyl cellulose polyvinyl pyrrolidone dextran and others Though many of them fit some of these criteria only one—*dextran*—fits enough to be seriously considered, and dextran fits all except one—No 8

Dextran has been known to sugar chemists for a century It was discovered in sugar beet preparations that had become infected with the bacterium *Leuconostoc mesenteroides* and similar organisms It was an undesirable substance so far as the sugar manufacturers were concerned Dextran is not a single substance but the name given to a group of polysaccharides of high molecular weight which break down

that overactivity of the spleen depends on the excessive action and possibly hyperplasia of the reticulo endothelial phagocytes and that the particular blood cells are collected and held in the splenic pulp The undue phagocytic activity has been shown by supra vital studies of cells from smears of splenic tissue taken after operative removal The fact that cells are being held in the pulp is demonstrated by giving a dose of adrenalin and by watching the changes in the blood count within the subsequent 10–60 mins when the appropriate cell can be found to have been squeezed out of the spleen For instance in splenic neutropenia the adrenalin test would raise the polymorph count in the blood In order to explain how cells come to be held in the splenic pulp the circulatory arrangements in the spleen have been studied Evidence has been produced for two possibilities (1) a closed circulatory system i e intact blood vessels from splenic artery through arterioles capillaries and venous sinuses to the splenic veins or (2) an open system in which there are apertures in the walls of the capillaries and venous sinuses and through these breaches interchange between the cells and fluid of the circulating blood and the relatively static fluid in the pulp can take place Doan and his colleagues support the open circulation theory and quote with approval the experiments of Bjorkman (1947) who showed that in the normal rabbit spleen starch particles of 1μ or less in diameter will pass from the blood into the pulp space whereas 85 per cent of particles measuring 5μ or more remain in the venous sinuses If the animal has an active infection or has been given a hæmolytic substance the 5μ particles will pass into the pulp and only about 50 per cent remain in the sinuses Doan (1949) therefore considers the splenic circulation to be semi open controlled by a mesh of variable size in the vessel walls In this way cells can be concentrated in the pulp and the sinuses and held in conditions approaching complete stasis It is known that under such conditions normal as well as old or fragile cells will be affected by the hæmolytic and phagocytic processes in the spleen and so the stage is set for excessive splenic sequestration and destruction of blood cells (2) Another school, supported by Damashek and his co workers while admitting that phagocytic activity of the spleen is important believes it to be less important than the action of the spleen on the bone marrow They consider that the spleen exerts a regulating influence on the bone marrow The regulation is thought to take the form of controlling the delivery of red cells granulocytes and platelets from the marrow and possibly their formation in the marrow When the spleen is overactive it *inhibits* these two functions so that in hypersplenism the marrow is full of cells that are not being delivered to the blood and in some series notably the platelets the proper development of cells may be inhibited The evidence for this theory is admitted to

into the alimentary tract in the gastric, intestinal and pancreatic secretions and that in the intestine it is finally split up and eliminated If confirmed, this would make dextran safe for all patients except those with intestinal obstruction or paralytic ileus

There is little doubt that dextran is a promising substitute the only one so far for plasma Practical physico chemical methods for controlling the molecular range are being worked out and it should be possible to prepare a reasonably constant solution with reasonably constant performance The Swedish workers have shown how useful dextran can be Both here and in the U S A interested bodies are at work to confirm and refine the Swedish results but the experimental stage is not yet completed

Recently another substance of the polyvinylpyrrolidone type has been introduced by Thrower and Campbell (1951) promising results are claimed but as with dextran the fate of all the injected material is not yet clear

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HYPERSPLENISM

Hypersplenism is the name given to a group of blood diseases in which clinical experience has shown that removal of the spleen will effect a significant amelioration of the disease All these hypersplenic syndromes are characterised by a *reduction* in the peripheral blood of erythrocytes granulocytes or platelets alone or together while in the bone marrow—the site of production of these cells—they are found to be present in normal or increased numbers It has to be explained therefore how the spleen by excessive activity brings about this result and two not necessarily mutually exclusive theories are current at present

(1) One school believes that the normal phagocytic action of the spleen for outworn red cells granulocytes and platelets becomes exaggerated Thus the peripheral cytopenia is caused by excessive destruction of these cells in the spleen while the active bone marrow represents a physiological response to the deficiency Doan and his co workers have consistently supported this idea They point out that the spleen has no specific cells its microscopical structure is made up of lymphocytes reticulo endothelial phagocytes connective tissue cells and enmeshed blood cells all of which are found elsewhere They consider

delivery and/or production of granulocytes and platelets with evidence of excessive destruction of red cells Doan does not recognise this division

For a diagnosis of hypersplenism the following features must be present —

(1) Cytopenia anæmia granulocytopenia thrombocytopenia
(2) *Palpable enlargement of the spleen*
(3) An active bone marrow showing good production of the types of cell that are diminished in the circulating blood

Experience has however shown that palpable enlargement of the spleen is not invariable in thrombocytopenic purpura In fact the presence of a really large spleen should make the physician consider that the case is one of secondary thrombocytopenia

When these points are established hypersplenism can be considered but as Dameshek and Estren point out hypersplenism is a functional and not an anatomical diagnosis and provides no certain guide to the histological changes in the spleen Every effort must therefore be made to exclude other diseases particularly Hodgkin s disease aleukæmic leukæmias and the like Even so after splenectomy examination of the spleen may show it to be effected by Hodgkin s disease follicular lymphoblastoma or other disease which has presented no other diagnostic clue The final diagnostic test is the success of splenectomy and the presence of only non specific hyperplasia of the spleen

Contra indications to splenectomy are —

(1) *evidence of acute or chronic bone marrow damage as from drugs*
(2) myelosclerosis or marble bone disease with splenic hæmopoiesis
(3) *aplastic anæmia*

Welch and Dameshek (1950) did four splenectomies in aplastic anæmia on the theory that the inhibiting influence of the spleen could be removed but they were not enthusiastic about the results

Apart from congenital spherocytic anæmia and thrombocytopenic purpura the primary hypersplenic syndromes are not common Doan (1949) reported that out of 270 splenectomies for hypersplenic syndromes in 17 years 13 were for primary splenic neutropenia and 11 for primary splenic pancytopenia Welch and Dameshek (1950) out of 220 splenectomies in ten years had 20 cases of primary splenic pancytopenia The results quoted by the pioneers are good in most cases the blood returns to normal and the associated clinical signs and symptoms disappear For example Dameshek and Estren quote the following cases —

be mainly clinical but there are some points in its favour difficult to fit in with the phagocytic theory For instance in thrombocytopenic purpura the blood platelet count sometimes rises an hour or so after the splenic vessels have been tied this is more easily explained by a release of inhibition than a sudden cessation of phagocytosis Again in purpura Dameshek and his school say that though megakaryocytes are present in the marrow few of them are producing granules but this finding has not been confirmed Damashek also considers the adrenalin test to be of little diagnostic value since it does not constantly produce the results expected How the spleen exerts this regulatory action is far from clear The experiments of Troland and Lee who claimed that the spleen secreted a substance acting on megakaryocytes and platelets and of Ungar who described two splenins with various actions have not been satisfactorily confirmed

Fortunately for the clinician though the rival schools differ about explanations they are largely agreed on the classification and treatment of the various hypersplenic syndromes There are two main divisions primary and secondary In the primary group the spleen alone is affected and there is no evidence of a more generalised disease The histology of the spleen shows hyperplasia of the normal elements—lymphocytes and reticulo endothelial cells—with perhaps some fibrosis but no abnormal or infiltrating cells are present In the secondary group the spleen has become enlarged and its elements hyperplastic through being involved in a more generalised disease e g Hodgkin s disease and other reticuloses lipoidoses Banti s syndrome or leukæmia

The syndromes of primary hypersplenism are —

(1) Congenital hæmolytic icterus (spherocytic anæmia)
(2) Splenic thrombocytopenia (thrombocytopenic purpura)
(3) Splenic neutropenia
(4) Splenic pancytopenia
 (*a*) with non hæmolytic anæmia
 (*b*) with hæmolytic anæmia

In the secondary group these syndromes occur in association with other diseases particularly those mentioned Acquired hæmolytic anæmia thought to be due to circulating agglutinins or hæmolysins is usually classed in this secondary group

Both Doan and Dameshek consider that congenital spherocytic anæmia cannot be wholly explained on the basis of abnormal red cells being excessively hæmolysed by normal hæmolytic processes Doan points out that particularly in hæmolytic phases of this disease transfused normal cells are rapidly destroyed presumably in the spleen Splenic pancytopenia is divided by Dameshek and Estren (1950) into two groups (*a*) due entirely to inhibition of delivery and/or production of red cells granulocytes and platelets and (*b*) inhibition of

prolonged and transfusions are needed infrequently but he gave a warning that the presence of blast cells in the blood is an absolute contra indication to splenectomy

There is thus reasonable evidence in favour of the clinical syndrome of hypersplenism and its logical treatment by splenectomy The explanations given may not be wholly convincing and there are relatively few reports of cases followed for more than two years after operation Nevertheless the diagnosis is worth serious consideration *if and only if all the features given above are present* There is little doubt that poor results will otherwise be obtained

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(1) *Splenic neutropenia* A woman of 42 had been chronically ill with weakness and recurrent infections for some time The spleen was three centimetres below the costal margin white cells were 1 530 p c mm with 22 per cent polymorphs no anæmia normal platelets The bone marrow showed a normal picture Four months after splenectomy the white cells were 7 800 p c mm with 64 per cent polymorphs and were at the same level 13 months later

(2) *Splenic pancytopenia with hæmolytic anæmia* A man of 53 had been ill for three years with jaundice pallor and weakness His liver was four and his spleen eight centimetres below the costal margin Red cells were 2 580 000 p c mm hæmoglobin 7 5 g p 100 ml white cells 1,350 p c mm with 46 per cent polymorphs platelets were less than half normal, reticulocytes were 10 2 per cent fæcal urobilinogen eight times normal The spleen was removed it weighed 1 000 grams and showed a non specific hyperplasia and fibrosis The blood count became normal and had remained so for five years

Others have not been so successful For instance Erf and Fry (1949) had a case that fulfilled all the requirements for splenic neutropenia including a positive adrenalin test After splenectomy the granulocytes in the blood rose sharply to a good level but soon began to fall slowly and after two years were only 900 p c mm Nevertheless the symptoms including recurrent mouth ulcers had not come back Hattersley (1947) has a case that did not respond at all to splenectomy but there was no splenomegaly In spite of reports like these it is clear that if a case satisfies the very rigid criteria set out above splenectomy has its place in the treatment even if the chances of relieving the symptoms are not 100 per cent

In recent years there has been a tendency to consider splenectomy in *secondary* hypersplenism recognising that the operation will not cure the primary condition but may ameliorate secondary blood changes particularly anæmia demanding frequent transfusion For example Doan quotes the case of a man with lymphatic leukæmia successfully controlled for some years with radio phosphorus He developed an acute anæmia and transfusions were of little help the marrow showed a normoblastic hyperplasia Splenectomy was accordingly performed and the anæmia remitted Control of the leukæmia was then resumed This point of view was emphasised at the 1950 International Hæmatology Conference T S Evans described three cases of follicular lymphoblastoma in which anæmia was relieved by splenectomy P S Hagen had eight leukæmic patients in whom the anæmia rather than the leukæmia was the disability splenectomy notably reduced their need for supporting transfusion R O M Berlin showed that the survival of the red cells in these anæmic leukæmia patients is much reduced After splenectomy survival is greatly

prolonged and transfusions are needed infrequently but he gave a warning that the presence of blast cells in the blood is an absolute contra indication to splenectomy

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(1) *Splenic neutropenia* A woman of 42 had been chronically ill with weakness and recurrent infections for some time The spleen was three centimetres below the costal margin white cells were 1 530 p c mm with 22 per cent polymorphs no anæmia normal platelets The bone marrow showed a normal picture Four months after splenectomy the white cells were 7 800 p c mm with 64 per cent polymorphs and were at the same level 13 months later

(2) *Splenic pancytopenia with hæmolytic anæmia* A man of 53 had been ill for three years with jaundice pallor and weakness His liver was four and his spleen eight centimetres below the costal margin Red cells were 2 580 000 p c mm hæmoglobin 7 5 g p 100 ml white cells 1 350 p c mm with 46 per cent polymorphs platelets were less than half normal, reticulocytes were 10 2 per cent fæcal urobilinogen eight times normal The spleen was removed it weighed 1 000 grams and showed a non specific hyperplasia and fibrosis The blood count became normal and had remained so for five years

Others have not been so successful For instance Erf and Fry (1949) had a case that fulfilled all the requirements for splenic neutropenia including a positive adrenalin test After splenectomy the granulocytes in the blood rose sharply to a good level but soon began to fall slowly and after two years were only 900 p c mm Nevertheless the symptoms including recurrent mouth ulcers had not come back Hattersley (1947) has a case that did not respond at all to splenectomy but there was no splenomegaly In spite of reports like these it is clear that if a case satisfies the very rigid criteria set out above splenectomy has its place in the treatment even if the chances of relieving the symptoms are not 100 per cent

In recent years there has been a tendency to consider splenectomy in *secondary* hypersplenism recognising that the operation will not cure the primary condition, but may ameliorate secondary blood changes particularly anæmia demanding frequent transfusion For example Doan quotes the case of a man with lymphatic leukæmia successfully controlled for some years with radio phosphorus He developed an acute anæmia and transfusions were of little help the marrow showed a normoblastic hyperplasia Splenectomy was accordingly performed and the anæmia remitted Control of the leukæmia was then resumed This point of view was emphasised at the 1950 International Hæmatology Conference T S Evans described three cases of follicular lymphoblastoma in which anæmia was relieved by splenectomy P S Hagen had eight leukæmic patients in whom the anæmia rather than the leukæmia was the disability splenectomy notably reduced their need for supporting transfusion R O M Berlin showed that the survival of the red cells in these anæmic leukæmia patients is much reduced After splenectomy survival is greatly

controlled trial had not been carried out Although the value of strepto mycin in the treatment of such lethal diseases as tuberculous meningitis and miliary tuberculosis could not be doubted its assessment in pulmonary tuberculosis with its varied nature and variable course was much more difficult Fortunately the Medical Research Council was able to begin in that year a controlled trial of the use of streptomycin in clinical pulmonary tuberculosis (M R C 1948) Patients were treated who had acute progressive bilateral pulmonary tuberculosis which was thought from the history and radiological appearance to be of recent origin There were 107 patients in the trial and they were divided into two approximately equal groups by random selection One group was treated by means of bed rest for six months while the other in addition to bed rest had 2 g of streptomycin intra muscularly each day in four injections at six hourly intervals In the majority of the second group streptomycin was given for four months Consideration of the results obtained after six months showed definite radiological improvement in 51 per cent of the streptomycin treated group but in only eight per cent of the other group It was noted that although radiological improvement occurred in patients with considerable cavitation streptomycin alone did not close large cavities

Various other important facts were observed during this trial Thus the greatest advantage from the use of streptomycin was in patients who were acutely ill Those who were afebrile who had a low sedimentation rate and not much cavitation often did just as well without streptomycin as with it Some light was also thrown on the question of the development of strains of tubercle bacilli resistant to streptomycin and on the relation of this to the results of treatment By the end of the second month of treatment most of the patients who still had tubercle bacilli in their sputum—the great majority—were expectorating strains of the bacillus which were resistant to the drug Those who had developed the most resistant strains more than 2 000 times that of the standard had the worst therapeutic results These observations about resistance were clearly very important since they implied that a patient being treated with streptomycin was unlikely to improve after the first two or three months of treatment and that once he had had such a course the drug was never again likely to help him Further there was considerable danger of disseminating strepto mycin resistant tubercle bacilli if patients had positive sputum after treatment

In an attempt to alter the development of streptomycin resistance the effect of various schemes of dosage was tried (Bignall *et al* 1950) In this trial the cases were of the same general type as those included in the first series Its result was essentially negative in that the degree

CHAPTER VIII

DISEASES OF THE CHEST

by

HOWARD NICHOLSON

Treatment of respiratory tuberculosis Chemotherapy tracheo bronchial tuberculosis Collapse therapy and pulmonary resection Pneumonia Classification and treatment Suppurative pneumonia Pulmonary infiltrations with eosinophilia

TREATMENT OF RESPIRATORY TUBERCULOSIS

Chemotherapy

SINCE the discovery of streptomycin (Schatz *et al* 1944) much work has been done to determine how it may be used to best advantage in the treatment of respiratory tuberculosis Many problems are still unsolved and it is certainly impossible to make a final assessment of its clinical use Nevertheless its value is established beyond question and it is possible to set out the general lines on which it is used A convenient method of doing this is to review some of the clinical studies that have been made of this drug thereby indicating the scope of its application and then to consider its use with methods of collapse therapy

In discussing the use of streptomycin in tuberculous tracheo bronchitis the condition will be described briefly since recognition of its importance is a real advance in the treatment of respiratory tuberculosis

Streptomycin Trials in Pulmonary Tuberculosis In 1946 after experimental studies and preliminary trials in clinical tuberculosis it was clear that streptomycin was almost certainly of great therapeutic value In the U S A where all the earlier work had been done a

streptomycin treatment The fundi should be examined frequently for choroidal tubercles although these are sometimes present without meningitis Lumbar puncture should be carried out at the beginning of treatment and repeated throughout the course Progressive renal lesions should also be watched for by the examination of the urine for tubercle bacilli by culture of 24 hour specimens at intervals through out treatment

At first treatment in these cases was carried on for three to four months but its cessation was not infrequently followed by relapse or the development of meningitis In this condition also *p* amino salicylic acid should be administered as well as streptomycin to reduce the incidence of streptomycin resistant strains of the bacillus The dosage should be of the order of 2 g of streptomycin per day given intramuscularly at twelve hourly intervals with 20 g of the sodium salt of *p* aminosalicylic acid in divided doses as suggested above This rate of administration should be maintained for six months at least

Streptomycin in Tracheo bronchial Tuberculosis Tuber culous inflammation of the mucosa of minor bronchi and bronchioles is very common in pulmonary tuberculosis particularly in relation to cavities and probably plays an important part in their development and their behaviour with collapse therapy Involvement of the trachea and major bronchi presents a different clinical problem and is conveniently considered separately under the term tracheo bronchial tuberculosis For practical purposes this implies that the bronchial changes are within the limits of bronchoscopic vision that is to say it includes the trachea and lobar bronchi and usually no more than the orifices of the segmental bronchi The incidence of this condition is difficult to estimate in this country In the U S A very high figures have been published Judd (1947) from broncho scopic findings in unselected tuberculous patients admitted to sanatorium found an incidence of 37 per cent in a series of 500 patients Other authors have published smaller figures the difference probably being mainly due to whether or not redness of the bronchial mucosa is accepted by itself as evidence of tuberculous bronchitis It seems probable that the usual incidence in all cases of active pulmonary tuberculosis in the U S A is about 11 per cent There have been no reports in this country based on bronchoscopic studies but clinical experience suggests that it is less frequent here

There are several methods by which tuberculous tracheo bronchitis may develop (Meissner 1945) The two most common are (1) by extension from a neighbouring pulmonary lesion through the sub mucosal lymphatic channels and (2) in association with primary infection ulceration of a bronchus by spread of the tuberculous

of resistance reached and the time of its emergence were not influenced by the dosage schedules used However the results of the trial suggested that one gram of streptomycin daily by one injection was as effective as the more elaborate methods of administering the drug

Before the results of this trial were published it had become clear that the most profitable method of attempting to delay the emergence of streptomycin resistant bacilli was by the use of other drugs with streptomycin At the present time *p* aminosalicylic acid is the only drug the use of which with streptomycin may be regarded as clinically established (Karlson *et al* 1949 M R C 1950a) This substance, which was applied to the treatment of tuberculosis by Lehmann (1946) has less therapeutic activity than streptomycin when used alone In combination with streptomycin it much reduces the incidence of streptomycin resistant tubercle bacilli and undoubtedly enhances the therapeutic effect The dosage used in the trial (M R C 1950a) was streptomycin, 1 g daily in one intramuscular injection, and the sodium salt of *p* aminosalicylic acid 20 g daily by mouth in four doses of 5 g This level of dosage was maintained for three months

It would be desirable to know the minimum dosage of *p* amino salicylic acid which will produce this suppression of streptomycin resistance but until this information is available it is probably best to keep to the sort of daily dosage set out above Further it is clearly wrong in the present state of knowledge to administer streptomycin alone other than in exceptional circumstances There is another point of considerable interest whereas in the earlier studies three months was regarded as the optimum period of treatment if streptomycin resistance is sufficiently delayed it may be advisable in some cases to maintain the combined treatment for six months or even longer

Streptomycin in Acute Miliary Tuberculosis Studies of the use of streptomycin in acute miliary tuberculosis have been carried out by several groups of workers for example Bernard and his colleagues (1949) and the Medical Research Council (1950b) The latter is of particular value in that the patients were observed for at least two years after the beginning of treatment These studies have shown that the mortality in this otherwise extremely fatal disease can be brought down to below 50 per cent The most serious complication is the development of tuberculous meningitis In a series of 70 cases (Bernard *et al* 1949) 44 also had tuberculous meningitis 17 being diagnosed before the commencement of treatment Of this group of 44, 37 patients died It is clearly important to recognise the existence of this complication as early as possible and to treat it by the additional use of intrathecal streptomycin Its development should be particularly watched for in patients who are acutely ill and whose temperature does not return to normal in the first month or two of

alteration of the function of mucous glands in the bronchial mucosa

(6) Cyanosis or dyspnœa in a patient with pulmonary disease This is associated with the bronchial obstruction and may take the form of what the patient may describe as asthma i e, paroxysms of dyspnœa

(7) On physical examination it may be found that breath sounds are markedly weak or absent over the whole or part of one side of the chest

(8) Radiological evidence this consists mainly of evidence of atelectasis of a lung lobe or segment

It is probably true to say that often the diagnosis of the condition will be certain enough from the presence of one or more of these features and the physician may decide to proceed with treatment before carrying out bronchoscopy Because of the bronchial anæsthesia necessary bronchoscopy might be expected to involve some risk of producing pulmonary spread In practice however the risk seems slight and most patients in whom the diagnosis is suspected should be bronchoscoped The bronchoscopic findings are varied and not always easy to interpret A bronchus through which sputum drains from an infected area is almost always red and œdematous This does not seem in fact to mean that there is tuberculous involvement of the mucosa Where however the redness and œdema are extensive perhaps involving the trachea or occur at a distance from the site of the pulmonary lesion then they should be regarded as evidence of tuberculous infiltration of the submucosal layer The presence of ulceration or granulation tissue is more easily interpreted Bronchial stricture in association with redness and œdema of the mucosa or with ulceration suggests that it is due to active inflammation whereas the presence of a normal mucosa suggests that the stricture is due to fibrosis following healing of an active lesion

The treatment of this condition by such measures as prolonged bed rest steam inhalation and topical application of silver nitrate solutions was unsatisfactory The introduction of streptomycin has completely altered the situation In the report of the trial carried out by the Veterans Administration (1948) great improvement or complete healing took place in between 80 and 90 per cent of cases treated with intramuscular injections of streptomycin Where there is also considerable uncontrolled pulmonary disease the bronchial disease may not heal or if it does so it may break down again That is to say it is necessary to regard the treatment of tracheo bronchial tuberculosis with streptomycin as part of a programme directed at the disease process as a whole Further the acute lesion may heal leaving a stenosed bronchus often leading to a fibrotic and bronchiectatic area

process from a nearby lymphatic gland The acute phase of the condition probably begins most commonly by infiltration of the submucous layer with tuberculous granulation tissue This is usually associated with congestion and œdema of the mucous membrane Ulceration of the surface may then occur, and tuberculous granulation tissue may in some cases proliferate from the ulcer into the lumen of the bronchus Healing of extensive lesions of this sort commonly produces some degree of fibrous stricture of the bronchus involved

The dangers of tuberculous tracheo bronchitis lie in the fact that the occlusion of major bronchi either in the acute or fibrotic stage may lead to atelectasis of large volumes of lung tissue This occurs without collapse therapy but since collapse procedures reduce further the lumen of an affected bronchus atelectasis is a frequent complication when these are used in the presence of tracheo bronchitis For example in a series of 40 cases with tuberculous involvement of major bronchi (Rafferty and Shields 1943) in which artificial pneumothorax treatment was used 17 patients developed lobar atelectasis shortly after induction In seven instances this was followed by infection of the atelectatic lung with anaerobic organisms In 12 patients atelectasis was complicated by tuberculous empyema and 11 of these died

While the final diagnosis of tuberculous tracheo bronchitis requires bronchoscopy it may be suspected when certain clinical and radiological features are present —

(1) The finding of tubercle bacilli in the sputum of a patient without an obvious pulmonary source i e no evidence of pulmonary infiltration or evidence only of what would otherwise be regarded as an entirely quiescent lesion The activity of a bronchial lesion need bear no relation to the extent or activity of related pulmonary disease and it is probable that lungs have been collapsed because they were thought to be the source of positive sputum which in fact came from a bronchus

(2) The persistence of sputum containing tubercle bacilli in a patient whose pulmonary disease has apparently been successfully treated by some measure of collapse therapy

(3) The presence of a wheeze which may be due to partial bronchial obstruction by a granuloma or stenosis The patient may complain of this or it may take the form of a persistent rhonchus localised to one part of the chest

(4) Severe cough out of proportion to what would be expected from the pulmonary lesion

(5) The patient may complain of great difficulty in bringing up sputum This may be due to increased viscosity because of

alteration of the function of mucous glands in the bronchial mucosa

(6) Cyanosis or dyspnœa in a patient with pulmonary disease This is associated with the bronchial obstruction, and may take the form of what the patient may describe as asthma i e paroxysms of dyspnœa

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of lung, and requiring treatment which will be discussed in a later section The dosage of streptomycin is usually 1 g each day by intramuscular injection with *p* aminosalicylic acid in the doses set out previously The drugs are usually continued for three or four months but this may be modified according to the rate at which the lesion clears and to the treatment adopted for associated pulmonary disease

Other Uses of Streptomycin in Respiratory Tuberculosis Streptomycin is used in the treatment of other forms of respiratory tuberculosis In tuberculous laryngitis it has proved extremely valuable and this dreaded and often terminal condition can now usually be brought rapidly under control Its use during thoracoplasty operations has been explored (Veterans Administration, 1948) and the conclusion reached that its prophylactic use is not justified On the other hand, the prompt therapeutic use of the drug when fresh areas of infiltration are observed or old quiescent lesions show evidence of activity, is almost certainly of value and adds to the safety of operative procedures Such information as there is about the effect of streptomycin in primary tuberculosis suggests that it is not of great value Similarly its use in cases of tuberculous empyema by intrapleural administration does not seem to have been of benefit, but tuberculous infection of the extrafascial thoracoplasty space has been successfully treated by this means

Streptomycin in Respiratory Tuberculosis A Summary As far as its use in respiratory tuberculosis is concerned streptomycin may therefore be said to be absolutely indicated in cases of miliary tuberculosis, and also in laryngeal tuberculosis and tuberculous tracheobronchitis In fresh areas of active disease occurring during collapse therapy it is extremely valuable It has not been shown to be of value in the treatment of primary tuberculosis or of tuberculous empyema

Its use in patients with progressive pulmonary tuberculosis is much less capable of precise definition In those with probable recent disease and with fever and raised sedimentation rate streptomycin *may reduce* the activity of the disease in a way that bed rest alone is unlikely to do, and so perhaps prepare the patient for collapse therapy In patients *who may be expected to do well on other lines of treatment for example* bed rest and collapse therapy it is probably inadvisable to give streptomycin because of its toxic effects and because even with the addition *of p aminosalicylic acid there is still some chance* perhaps as much as ten per cent of producing streptomycin resistance in the infecting organisms In afebrile patients with chronic fibrotic disease the drug *is not likely* to be of much value To those who do not fall into these groups, streptomycin should only be given after careful consideration and if it seems likely that it may be fitted into some effective scheme

of treatment The special case of the so-called tension cavity will be discussed later

Toxicity of Streptomycin The toxic effect most frequently met with in the administration of streptomycin over long periods has been disturbance of vestibular function The commonest symptom of severe toxicity is a sensation of giddiness in the upright position, sometimes associated with nausea and vomiting This state lasts a few days and is then usually replaced by a chronic condition in which only sudden movements produce vertigo In time this difficulty is usually overcome and the eyes become of great importance in maintaining balance This effect was frequently met with in the earlier days of streptomycin treatment when larger doses were used With a daily dose of 1 g the incidence of subjective vertigo is of the order of 12 per cent (M R C 1950a) It usually occurs after a total of about 60 g has been given and is only rarely severe enough to interfere with treatment Deafness also occurs during streptomycin treatment but in practice is met with extremely rarely Dihydrostreptomycin which is said to disturb vestibular function less frequently than streptomycin seems to cause deafness more often

Local reactions are common Following an intramuscular injection pain and swelling at its site may develop immediately This reaction lasts usually for less than 24 hours and requires no more treatment than the use of another situation for the next injection

Cutaneous eruptions due to the development of allergy occur in two to nine per cent of all cases (Bunn and Westlake 1949) The rash is seen after about ten days from the beginning of treatment and is usually maculopapular in form and itchy Sometimes it is associated with fever and joint pains Streptomycin can usually be continued in spite of the rash which gradually disappears Anti histamine drugs are useful in controlling the itching When there are severe general symptoms and if the eruption progresses then streptomycin should be stopped The patient can often be desensitised by gradual increase from a small tolerated dose and the course resumed Dermatitis occurring mainly on the hands of persons handling the drug for long periods has been reported frequently If possible such a sensitive individual should cease to be in contact with the drug but if necessary desensitisation can be carried out Although other undesirable effects have been described, these are the main ones met with in practice

Toxicity of *p* Aminosalicylic Acid Gastro-intestinal upsets are commonly produced by this drug A large proportion of patients experience nausea and many vomit Diarrhœa and abdominal pain are also not infrequent In the majority it is possible to continue its administration and the symptoms decrease Occasionally it is

necessary to reduce the dosage and the maximum amount that can be tolerated should be given Rashes and febrile reactions are occasionally seen, and are dealt with on the same lines as those which occur with streptomycin Indeed as the drugs are now usually given together, it may be impossible to tell which drug is responsible

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Collapse Therapy and Pulmonary Resection

Although recently overshadowed by the development of chemo therapy there has been a steady advance in the understanding of the proper use of collapse therapy It is unfortunately impossible to demonstrate statistically that collapse therapy in pulmonary tuberculosis has advantages over the older methods of bed rest and the sanatorium regime There have been many papers comparing the results of collapse therapy—usually artificial pneumothorax—with the results of treatment with rest and graduated activity Bentley (1936) compared 677 patients treated with artificial pneumothorax in the London County Council s anti tuberculosis scheme with 3 329 who were treated by conservative methods only He made it clear that a perfect control series could only be provided by selecting an adequate number of patients who were all regarded as suitable for

pneumothorax treatment and then dividing them by random selection into two equal groups One group would be treated by the older general measures and the other with artificial pneumothorax in addition His series did not fulfil these criteria but there was sufficient similarity of classification and environment between the two groups to make a broad evaluation He concluded that the survival rate was approximately 20 per cent higher in the pneumothorax group than in those conservatively treated *Bentley s figures related to artificial pneumo* thoraces induced before the end of 1930 Assuming as he did that the treatment can be applied to only ten per cent of patients it will be seen that the gross statistics of treatment will be little altered by its use The fact that it is generally regarded as unjustifiable to conduct a trial of the use of collapse therapy while leaving untreated a control series suggests that the majority of clinicians have no real doubt of the value of such treatment

The remainder of this section is concerned mainly with discussing the selection of patients for treatment It is convenient to consider first the indications for collapse therapy in general and then to refer to the circumstances which play a part in the choice of the various methods available

The indication for collapse therapy which is generally agreed upon is the presence of cavitation Even where the sputum on repeated smear examinations cannot be shown to contain tubercle bacilli provided there is adequate evidence that the disease is tuberculous cavitation should still be regarded as indicating the need for collapse therapy Many cavities will heal on bed rest alone In general where collapse measures are feasible and particularly in patients who must return to an active life such closure or the possibility of it should not defer collapse therapy The use of collapse therapy in the absence of cavitation is more controversial Few would withhold this form of treatment from patients with infiltration which progresses in spite of bed rest or on return to a restricted life after bed rest and a sanatorium regime or from whose sputum tubercle bacilli are repeatedly recovered In young patients with small areas of infiltration seen on routine radiography or in radiographs taken after upper respiratory infections and from whom tubercle bacilli are not recovered the situation is more complicated Some of these lesions are not tuberculous (*cf* Ramsay and Scadding 1939) but are transient pneumonias which disappear after two or three weeks Of those lesions presumed to be tuberculous it will be possible in some to have reasonable evidence that they are active There may be radiological evidence that the le recently appeared or on observation of the patient in bed t a low grade fever or a persistently raised sedimentation circumstances the first line of treatment should be three

necessary to reduce the dosage, and the maximum amount that can be tolerated should be given Rashes and febrile reactions are occasionally seen, and are dealt with on the same lines as those which occur with streptomycin Indeed, as the drugs are now usually given together it may be impossible to tell which drug is responsible

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The danger here is that the induction of artificial pneumothoraces is frequently followed by the development of pleural effusions and tuberculous empyemata In view of the results of streptomycin treatment of acute bronchopneumonic tuberculosis it is preferable to treat such acutely ill patients with streptomycin and *p* aminosalicylic acid as outlined previously This is usually followed by a rapid decrease in the constitutional disturbance and by some resolution of the pneumonic process Often after about six to eight weeks this de fervescence may have progressed far enough to allow induction of a pneumothorax It is usual to continue the chemotherapy for four to six weeks after induction Rafferty also includes in the temporary group those cases with active tracheo bronchial tuberculosis without marked stenosis The recognition and treatment of this condition has already been considered and if the acute phase heals without fibrous stenosis then the induction of an artificial pneumothorax becomes correspondingly safer

Among permanent contra indications Rafferty includes the presence of a large peripheral cavity because of the danger of rupture of such cavities into the pleural space The division of adhesions to these cavities may destroy the blood supply of part of the wall with resulting necrosis and rupture This view probably applies particularly to cavities which occupy most of the apex of a lung To some extent it may be modified if it is possible to reduce the size of a cavity before beginning collapse therapy For example Dilwyn Thomas (1950) has introduced a method which he calls postural dependency whereby the patient is placed in a position of reversed postural drainage in relation to the cavity If he is kept constantly in such a position considerable decrease in cavity size usually takes place in a few weeks Streptomycin treatment also sometimes produces diminution in the size of cavities presumably mainly in those with a marked distension factor in their development the mechanism of this will be referred to later By such means as these it may become possible to induce pneumothoraces without courting disaster

Extensive fibrous disease is also a permanent contra indication The danger here is mainly that in most of such cases considerable pleural adhesions prevent satisfactory collapse It cannot be doubted that the more extensive the operative division of adhesions the greater the incidence of complications particularly pleural effusion and tuberculous empyema It is in relation to this type of disease that clinical judgment as to the practicability of other types of treatment and in the assessment of the risks involved in using artificial pneumo thorax is particularly important

Fibrous stenosis following tuberculous tracheo bronchitis is the final condition in the group of permanent contra indications The dangers

followed by three months of gradually increasing activity Where these measures fail, collapse therapy is indicated (cf Amberson, 1937) In those patients with small uncavitated lesions in whom no evidence of activity can be found frequent radiographs while the patient continues his work may show progression and the need therefore for bed rest In others the absence of radiological change and the continued absence of signs of activity may indicate a quiescent lesion In older patients there is the added possibility that the lesion may be a bronchial carcinoma but where this can be excluded with reasonable certainty the indications for collapse therapy in these cases without cavitation remain much the same as in the younger group

As treatment for hæmoptysis occurring in pulmonary tuberculosis collapse therapy is used less freely than formerly Except in very severe cases in which other methods have failed, it is best to treat the lung condition on its own merits and not be forced into the use of therapeutic collapse as an emergency measure There is also the danger that the presence of aspirated blood in the bronchial tree may lead to extensive atelectasis if the bronchial lumen is reduced and the cough mechanism impaired by such procedures The presence of tuberculous laryngitis and enteritis, since they depend on the production *of tubercle bacilli from the lungs furnishes additional indication for* collapse therapy Primary tuberculosis alone or with related phenomena such as pulmonary atelectasis except when it progresses and takes on the features of the adult type of disease does not require collapse therapy Further tuberculosis in association with pneumoconiosis is not usually treated in this way because of the low respiratory reserve Clearly the presence of severe tuberculous or non tuberculous disease elsewhere in the body may exclude collapse therapy

Artificial Pneumothorax It is probably true to say that in practice artificial pneumothorax is regarded in cases where it is likely to be successful as the most valuable form of collapse therapy This is so mainly because of its applicability to disease in most parts of the lung the relative simplicity of the procedure and the absence of chest wall deformity Therefore having decided on the general suitability of the patient for collapse therapy it is reasonable first to consider whether his disease may be treated by means of artificial pneumothorax Following Rafferty (1947) contra indications to this form of treatment may be considered in two groups temporary and permanent The temporary group comprises conditions which may resolve and permit induction of a pneumothorax later Rafferty includes in it first of all tuberculous pneumonia It is probably reasonable to class with this those more acute varieties of the disease which have extensive infiltration associated with fever considerable loss of weight a high sedimentation rate and other evidences of constitutional disturbance

be to produce an anatomically perfect pneumothorax, or one in which adhesions if present are not in relation to the diseased area In general a pneumothorax should be continued only if it is of this type except that again it may sometimes be necessary to maintain a less than satisfactory pneumothorax where other procedures are not possible

Bilateral Disease These considerations as to suitability for and the maintenance of artificial pneumothorax apply also to bilateral disease When the condition in both lungs is suitable bilateral pneumothoraces should be undertaken Any adhesions in the first side to be induced should be divided and a satisfactory and stable pneumothorax achieved before the second side is induced Other combinations such as pneumothorax on one side and some other form of collapse therapy on the other may be possible The decision whether bilateral disease is too extensive for such measures calls for great clinical judgment In this the possible effect of long continued streptomycin must be remembered

Duration of the Artificial Pneumothorax This question has been studied by many authors (e g Hurst and Schwartz 1942) While there is no firm rule a period of more than three years is probably advisable and if there was cavitation before treatment it is best continued for five years The duration of collapse should be calculated from the time at which the pneumothorax was made satisfactory with cavity closure and disappearance of tubercle bacilli from the sputum

The Tension Cavity It has been shown at autopsy that in many bronchi draining cavities there is evidence of tuberculous inflammation of the mucosa The importance of this in the development and maintenance of cavitation in the lung was pointed out by Coryllos and Ornstein (1938) Bronchi undergo respiratory changes elongating *and dilating in inspiration Normal bronchi remain patent even at the* end of expiration When a small bronchus is partly blocked by tuberculous inflammation its lumen may be very small or may be completely occluded in expiration In a small bronchus leading to a cavity a valvular obstruction may be produced which allows air to enter the cavity in inspiration but prevents its escape in expiration By this means a cavity may be inflated to a size out of proportion to the amount of lung tissue destroyed When this mechanism is highly developed a tension cavity is produced This is spherical in shape with a thin wall and often a fluid level and it may be very large. Coryllos also put forward the view that complete blocking of the draining bronchus so that it is closed in inspiration and expiration leads to closure of the cavity

From this point of view the condition of the bronchi draining a cavity may affect its treatment by artificial pneumothorax in various ways If the bronchial lumen is normal or almost so then after

involved have already been discussed, and possible methods of treatment will be considered in a later section

Pleural Adhesions There are probably few clinicians who follow the practice of Laird (1945) in carrying out a thoracoscopic examination in every case of artificial pneumothorax Nevertheless, the value of thoracoscopic division of pleural adhesions can hardly be disputed Many papers have been published dealing with the operation (e g, Brock, 1938) and leave little doubt that the incidence of serious complications after the operation is less than in patients in whom artificial pneumothoraces are continued with undivided adhesions Probably the most usual practice is to carry out thoracoscopy with a view to the division of adhesions in most cases The exceptions will be mainly those in which cavity closure and disappearance of tubercle bacilli from the sputum have occurred and in which adhesions are not visible on radiographic study Some clinicians consider that in cases of cavitation involving the apical segment of the lower lobe thoracoscopy should never be omitted because of the difficulty of being certain from radiographs whether or not there are adhesions to the posterior surface of the lung Such views are supported by Crofton (1949) who showed that the treatment of these cavities with adequate artificial pneumothoraces produced satisfactory results

The time after induction at which adhesions should be divided has been studied by Antilla (1947) His conclusion is that there is a greater chance of success if the operation is performed early—in his series before the fortieth day after induction Most thoracic surgeons would agree with this view The operation is usually carried out in the first month because it is then technically easier before pleural thickening occurs and if the adhesions can be divided the pneumothorax is the sooner effective

Technical problems relating to the suitability of adhesions for division need not be considered here The physician should however, again consider the question of the practicability of other forms of treatment in order to give the surgeon some indication of the justifiable extent of the operative procedure If there is no contra indication to thoracoplasty as an alternative measure then it is clearly unreasonable to subject the patient to the risks involved in the division of very extensive adhesions On the other hand such risks may have to be taken if, because of the nature of the disease, such an alternative is not feasible Papers such as that by Livingstone (1939) who reviewed a series of patients developing active disease within two years of re expansion of pneumothoraces and found that recrudescence was commoner in patients who had not had anatomically satisfactory collapse leave little doubt that adhesions to diseased lung should be divided if possible Indeed the aim in all cases should

applied only to patients with old disease and considerable fibrosis Indeed Price Thomas and Cleland (1942) demonstrated that the best results were obtained when the disease had probably been present for less than six months In disease which had been present for many years the operative risks were greater and the chances of closing the hard walled cavities less Other factors contributing to good results were the absence of much constitutional disturbance and the presence of stable disease Nowadays many patients with progressive disease and constitutional symptoms may achieve this stable condition after chemotherapy and so become suitable for thoracoplasty

Until quite recently it was usual in all cases requiring collapse therapy to attempt first of all to induce an artificial pneumothorax There is now considerable agreement that there are many cases in which thoracoplasty should be used as the primary measure of collapse treatment These are the varieties already considered in relation to the permanent contra indications to artificial pneumothorax In this category were included cases of large apical cavitation and of extensive fibrous disease The presence of fibrous stenosis of major bronchi was also considered to be a permanent contra indication to artificial pneumothorax In cases with incomplete stenosis and upper lobe disease thoracoplasty is effective treatment (Alexander *et al* 1942) The question of resection in cases with more complete stenosis and lower lobe disease will be referred to later

Apart from these cases in which thoracoplasty would be regarded as the first measure there are those in which artificial pneumothorax treatment has been unsuccessful In some induction is impossible because of widespread adhesion in others the pneumothorax is abandoned because of failure to establish a satisfactory one In general thoracoplasty is the next step but there are certain other factors to be considered —

(1) The fact that the disease is early need not contra indicate the operation It is not usual now to attempt artificial pneumothorax treatment in patients with rapidly progressive disease and patients who have been regarded as suitable for artificial pneumothorax from the point of view of their general condition will usually be suitable also for thoraco plasty

(2) In some instances it will have been thought reasonable to attempt artificial pneumothorax treatment in the absence of cavitation Although this is not a universal view most authorities will not go on to thoracoplasty in the absence of cavitation and a positive sputum

(3) Cases with cavitation in the apex of a lower lobe and disease of the upper may be treated by means of an extensive

induction of a pneumothorax and the freeing of adhesions between the cavity and the chest wall, the cavity may close as part of the general retraction of the lung At the other extreme, where the bronchial lumen is severely reduced, a pneumothorax may allow it to close completely so closing the cavity A less severely affected bronchus when reduced in size after induction of a pneumothorax may develop a valvular mechanism or maintain an already existing one In some instances cavities which were already recognisable as being of the tension type may enlarge after the beginning of a pneumothorax, and also cavities apparently not of this type may take on its characteristics The danger of a tension cavity under an artificial pneumothorax is that rapid enlargement may result in its rupture into the pleural space and the development of a tension pneumothorax and a tuberculous empyema

In general the pneumothorax treatment of already established tension cavities has met with little success and other methods such as thoracoplasty catheter drainage (Monaldi, 1939) or resection have been used It is likely however that in view of the effect of streptomycin treatment on bronchial tuberculosis it may be possible by its use to overcome the valve mechanism in some cases In practice streptomycin has certainly reduced the dangers inherent in the treatment of this sort of cavity and in many instances made pneumothorax treatment possible

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Thoracoplasty Sauerbruch s original indications for thoracoplasty were briefly, the presence of strictly unilateral predominantly fibrotic disease in a non toxic and afebrile patient In recent years these indications have been widened a good deal, and the operation is no longer



Fig. 1a.



Fig. 1b.

Figs. 1a and 1b. Postero-anterior and right lateral radiographs showing extensive tuberculous infiltration of the right upper lobe with a cavity. There is consolidation of the posterior segment. On bronchoscopy tuberculous bronchitis of the right upper bronchus was found.

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regard it as a preparation for thoracoplasty, as was advocated by Reid (1946) The present indications may be summarised in the following way The disease should be regarded as suitable for artificial pneumothorax treatment which because of pleural adhesions has not been established Upper zone cavitation should be present, but not large or peripheral in type, and there should be little fibrosis and no obvious fibrous thickening of the pleura In the majority of patients presenting these features thoracoplasty is the operation of choice, but in a few extrapleural pneumothorax may be preferred These few are (1) children particularly under the age of 14 (Reid, 1946) in whom thoracoplasty tends to produce severe skeletal deformity, (2) those with low vital capacity since it has been shown (Gaubatz, 1938) that extrapleural pneumothorax reduces this less than thoracoplasty, and (3) in some of those with extensive disease on the other side requiring thoracoplasty and where it may not be thought possible to carry out a bilateral thoracoplasty

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Phrenic Crush and Pneumoperitoneum In recent years there has been considerable interest in the place of pneumoperitoneum in the treatment of pulmonary tuberculosis (Banyai 1946 Keers, 1948) Pneumoperitoneum must be regarded as a means of augmenting the ascent of the diaphragm produced by phrenic paralysis and not be used as a sole method of treatment Since the usually temporary paralysis of the diaphragm produced by phrenic nerve crush is almost invariably carried out in preference to evulsion the indications for phrenic crush and pneumoperitoneum must be considered together To a considerable extent these depend on the circumstances in which treatment is being carried out If surgical assistance in adhesion division and the performance of thoracoplasties and other operative measures is not available then this form of treatment may offer the only hope of controlling a diseased lung and may indeed be preferable to the maintenance of an inadequate pneumothorax with undivided adhesions Conditions for which it may be used with most likelihood of success can be divided into those in which it is a temporary measure and those in which it is the definitive line of treatment In the first group are those patients with acute disease regarded as too ill for artificial pneumothorax In some of these phrenic paralysis and pneumoperitoneum may supplement chemotherapy in preparation for



Fig. 21a.



Fig. 21b.

Figs. 21a and 21b. Postero-anterior and right lateral radiographs showing extensive tuberculous infiltration of the right upper lobe with a cavity. There is consolidation of the posterior segment. On bronchoscopy tuberculous bronchitis of the right upper bronchus was found.

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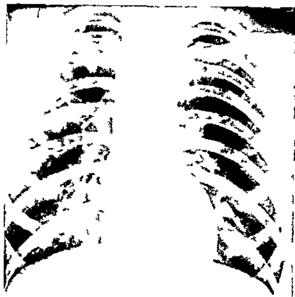


Fig 21c Postero anterior radiograph of same patient showing considerable resolution after treatment with streptomycin and p aminosalicylic acid for six weeks The right upper bronchus appeared normal on bronchoscopy

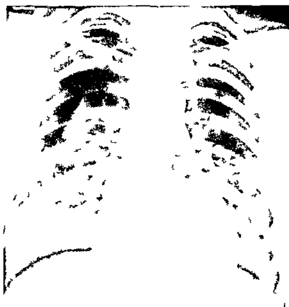


Fig 21d Postero anterior radiograph of same patient after establishment of an artificial pneumothorax The lung is free after thoracoscopy and cauterisation of adhesions



FIG 2"a Postero-anterior radiograph howing mainly fibrotic tuberculous disease of the upper part of the r ̥l t lung with several small cavities This was regarded as unsuitabl for treatment by means of artificial pneumothorax.



FIG ."b I ostero-anterior radiograpl of same patient after partial thoracoplasty

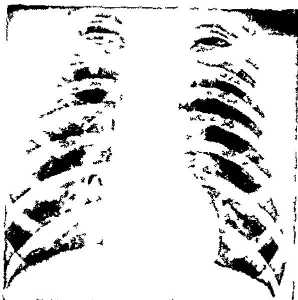


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Fig 21d Postero anterior radiograph of same patient after establishment of an artificial pneumothorax The lung is free after thoracoscopy and cauterisation of adhesions



Fig 2 a Postero-anterior radiograph showing mainly fibrotic tuberculous disease of the upper part of the right lung with several small cavities. This was regarded as unsuitable for treatment by means of artificial pneumothorax.



Fig 2 b Postero-anterior radiograph of same patient after partial thoracoplasty

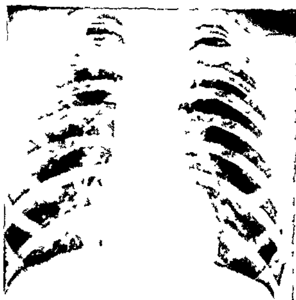


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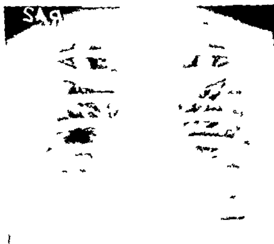


Fig 23c I osterо-anterior rad ograj h of same pat ent after left lower l bectomy The diaphragm is l igh in position and there is a lar,e ga tric flu l lev l

(To face Figs. 23a and b



Fig 23a Postero anterior radiograph showing a tuberculous pneumonia which occupied the left lower lobe Two large cavities which were in the apical segment of the lobe can be seen The left lower lobe bronchus was inflamed and the patient was acutely ill



Fig 23b Postero anterior radiograph of same patient after treatment with streptomycin and *p* aminosalicylic acid for three months The cavitation is less evident *The left lower lobe bronchus was stenosed* but did not show evidence of active inflammation

other collapse measures In this group also may be included some patients in whom contralateral disease may be controlled by this means in preparation for thoracoplasty on the side mainly affected

In the second group are —

(1) Those patients in whom it is used to supplement an incomplete pneumothorax The type of pneumothorax with which it is chiefly successful is that in which the lung is free laterally but adherent to the upper mediastinum and diaphragm If the diaphragm can be made to rise in the chest the upper part of the lung can be further relaxed

(2) Some patients with cavitation in the apex of a lower lobe If they have no bronchostenosis and little other disease and if it has been impossible to establish a satisfactory artificial pneumothorax this method may sometimes be successful

(3) Those patients with progressive non cavitated infiltration considered suitable for artificial pneumothorax treatment but in whom its satisfactory establishment has been impossible Since it is usually thought inadvisable to proceed to thoraco plasty phrenic crush and pneumoperitoneum will often provide some measure of control

The use of the method for patients in the second group and for those with more extensive disease is probably mainly a matter of circumstances and personal judgment Lower zone disease is likely to be controlled more effectively than disease in the apex and the treatment is not entirely safe to apply in the presence of tracheobronchial disease since complete obstruction of major bronchi can be produced with atelectasis of the related part of the lung

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PNEUMONIA

Classification In a study of 351 cases of pneumonia admitted to the Central Middlesex County Hospital between 1942 and 1944 Humphrey and his colleagues (Humphrey *et al* 1948 Glover *et al* 1948) found that in 298 instances the disease was due to specific bacterial infection In 278 of these the infection was pneumococcal and in 20 it was due to other pathogenic bacteria In the remaining 53 patients the pneumonia was not apparently caused by specific bacterial infection As these authors point out there has recently been great interest in those pneumonias which are not due to the classical bacterial agents In part this interest has been stimulated by the use of chemotherapeutic substances which made it advisable to know whether the infecting organisms were susceptible to the drug

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used Also with the general use of radiography in respiratory infections it was found that many patients who did not present the symptoms and signs usually associated with pneumonia had nevertheless pulmonary shadows which could only be interpreted as consolidation Whereas in those pneumonias due to specific bacterial infection a precise ætiological nomenclature is available *in this other group*, because of the absence of knowledge of specific infecting agents nomenclature has caused considerable difficulty To many such cases the name 'primary atypical pneumonia has been applied and it has often been assumed that they are due to a specific virus This assumption was examined by Scadding (1948) in an article on the pneumonias associated with epidemic respiratory infections

The evidence in favour of a specific viral ætiology is based chiefly on the following observations —

(1) Groups of similar cases occur together suggesting the presence of a single infecting agent and the bacteria usually associated with pneumonia are not found in the sputum
(2) Autopsies on patients dying during outbreaks of this type of pneumonia have certain similar features namely infiltration of the interstitial tissues with mononuclear cells and alveolar exudates containing similar cells In association with this is seen a desquamating bronchitis in the larger bronchi frequently with a purulent exudate Bacteria if present are chiefly found in the larger bronchi These changes are unlike those seen in the recognised bacterial pneumonias
(3) Some outbreaks of this sort have been accompanied by a marked rise in the cold agglutinin titres of the sera of a third to a half of the patients This test is carried out (Turner *et al* 1943) by allowing dilutions of serum to stand overnight at 4° C with a suspension of fresh washed human red cells and recording the highest dilution at which macroscopic agglutination occurs In the 83 cases recorded by Turner and his colleagues more than half had an agglutinin titre of 1 32 or higher On the other hand in other series of such cases the phenomenon was not seen and although cold agglutination may well be related to virus infection the evidence in connection with it does not suggest that these pneumonias form a uniform group

The evidence against a single specific viral ætiology in these cases is based on the following considerations —

(1) The outbreaks described under this term have varied considerably and have included at one extreme mild cases of upper respiratory infection associated with transient pulmonary consolidations and at the other cases with severe

general illness as well as pulmonary consolidation In addition in some outbreaks specific ætiological agents were probably involved—for example the cases of rickettsial Q fever reported from the Mediterranean area during the late war (Commission on Acute Respiratory Diseases 1946)

(2) Attempts to isolate a virus from such cases have rarely been successful and a constant virus has not been isolated

(3) Many of the cases commonly included in this group are similar to those described by Ramsay and Scadding (1939) who found among a large number of new patients radiographed at a tuberculosis clinic 21 in whom relatively trivial catarrhal symptoms were associated with transient areas of pulmonary consolidation In their discussion of the nature of these lesions they refer to the work of Quinn and Meyer (1929) who showed that iodised oil introduced into the noses of sleeping subjects could be demonstrated radiographically in alveoli the next morning They also quoted Gunn and Nungester (1936) who in the course of attempts to produce experimental pneumococcal pneumonia in rats were able to produce transient consolidation by the intrabronchial injection of mucin alone It seemed therefore possible that mucus either from the upper respiratory tract or of bronchial origin might obstruct bronchi or bronchioles and produce the sort of mild transient pneumonia which they had described These transient shadows are often seen in patients with chronic bronchitis asthma or chronic abnormalities of the upper respiratory tract causing excessive secretion as well as with acute respiratory catarrh In view of this and the sporadic nature of the cases described it must be considered unlikely that they were due to infection with a specific virus and probable that they represented an infected segmental or lobular atelectasis i e aspiration pneumonia The sputum in these cases usually contains only those types of bacteria which may be found in the normal upper respiratory tract *none of which is specifically invasive for the lungs* In these circumstances the bronchial or bronchiolar block producing atelectasis beyond the obstruction is the more important factor The inflammatory reaction produced in the airless lung by the bacteria present in the blocking mucus plug is slight and rapidly proceeds to complete resolution

Scadding (1948) concludes that the name primary atypical pneumonia should be abandoned Some cases of pneumonia not due to specific bacterial infection may be due to specific infecting organisms of other types e g rickettsial and should be labelled

appropriately When the evidence suggests a non specific infected atelectasis associated with respiratory catarrh the term "aspiration pneumonia" should be used There remain a number of cases without pre existing respiratory catarrh which particularly in the presence of a local outbreak of similar cases may be thought to be due probably to an unidentified virus these should be labelled "pneumonia presumably due to an unidentified virus

Using the term pneumonia to mean any inflammatory consolidation of the lung Scadding (1946) has put forward a classification of the acute pneumonias which is based on considerations like those set out above He pointed out that the older nomenclature was based on anatomical features and that this was satisfactory as long as only supportive treatment was available His classification divides the acute pneumonias into two main groups those due to the action of a virulent organism on a susceptible host the acute specific pneumonias and those which are essentially infected atelectases, the aspiration pneumonias A classification based on Scadding s is set out below

Classification of Acute Pneumonias

1 Acute Specific Pneumonias	
(A) Bacterial	
Str pneumoniae	Lobar or croupous pneumonia
Str haemolyticus	
Friedlander s bacillus	
Staph aureus } *H influenzae* }	{ Often in association with influenza virus
M tuberculosis	Tuberculous pneumonia
B anthracis	Wool sorter s disease
P pestis	Pneumonic plague
(B) Virus	
Measles } Influenza }	{ In man these viruses are usually associated with bacterial infection
Ornithosis	This group includes psittacosis
Other unidentified viruses	Some cases of primary atypical pneumonia
(C) Rickettsial	E g in Q fever
(D) Plasmodial	In P falciparum malaria
2 Aspiration Pneumonias	
(A) Diffuse	Bronchopneumonia
(B) Localised	
(*a*) Transient consolidation associated with mild infection	Some cases of primary atypical pneumonia

(*b*) Suppurative processes of varying severity associated with more severe infection

Scadding points out that the two main groups are not mutually exclusive The organisms most commonly found in the sputum of patients with aspiration pneumonia are *Str viridans* non hæmolytic streptococci pharyngeal neisseriæ and sometimes small numbers of the less invasive types of pneumococcus These are bacteria which may be found in the normal upper respiratory tract If however one of the specifically invasive organisms is present in the aspirated secretions then what began as an aspiration pneumonia may develop into an acute specific pneumonia It is clear therefore that this classification cannot be regarded as absolute or complete but it will be found to provide a useful and practical way of thinking about individual cases

Treatment The main application of this classification is in the consideration of treatment In the acute specific bacterial pneumonias the most important measure is the use of suitable chemotherapeutic or antibiotic agents Pneumococci and hæmolytic streptococci are usually sensitive to sulphonamides—sulphamezathine because of the solubility of acetyl derivative being the one most frequently used Penicillin also is usually effective against these organisms and must be employed against *Staph aureus* where this is sensitive Streptomycin is effective against Friedlander s bacillus penicillin having no effect In order to use these drugs to the best advantage it is necessary to isolate the causal organism from sputum or if there is none from a throat swab Blood culture should be carried out before beginning treatment of a severely ill patient The sensitivity of the organisms to the available agents can be determined and the most suitable one used The newer antibiotics such as aureomycin and chloramphenicol are useful in the treatment of pneumonias due to bacteria resistant to penicillin and the sulphonamides

The pneumonias which occur in influenza virus infection are almost always associated with bacterial infection also and chemotherapy may play a useful part in their treatment The pneumonia associated with *Staph aureus* and influenza virus infection is recognised as being almost invariably fatal Walshe (1950) reports such a case in which the staphylococcus was relatively insensitive to penicillin Treatment with chloramphenicol and massive doses of penicillin was followed by recovery of the patient and clearing of the pneumonia Ornithosis, as well as those pneumonias apparently due to unidentified viruses is reported as responding to treatment with aureomycin or chloramphenicol The pneumonias associated with rickettsial infection also respond to these drugs

The treatment of the aspiration pneumonias depends mainly on the severity of the condition. Mild cases of transient consolidation associated with upper respiratory catarrhal infections need no special treatment. When the inflammatory process in the lung is more severe, then a combination of chemotherapeutic and physical methods is called for. The patient should be encouraged to cough in order to expel the infecting material from his bronchial tree. He should lie in bed in such a position that the secretions may drain from the infected region and this drainage may be aided by gentle percussion of the chest. In addition the sputum should be cultured and the infecting organisms treated by whatever chemotherapeutic agents are suitable. Aureomycin and chloramphenicol are both effective against most of the organisms associated with this sort of pneumonia and will no doubt be freely used in its treatment. The treatment of the more suppurative types of aspiration pneumonia and of acute lung abscess will be considered in the next section.

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SUPPURATIVE PNEUMONIA

Suppurative pneumonia is a term which may be applied to those inflammatory consolidations of the lung which proceed in whole or in part to suppuration. It is useful to consider these suppurative affections of the lung as forming a group capable of being sub divided as follows: (1) those specific pneumonias in the course of which suppuration occurs, (2) pulmonary suppuration in relation to bronchial carcinoma, and (3) non specific suppurative pneumonia (Nicholson 1950a and b).

The Specific Pneumonias Associated with Suppuration. The most important specific pneumonias which are associated with

suppuration are those due to the pneumococcus *Staph aureus* and Friedlander's bacillus In pneumococcal lobar pneumonia lung abscess is not common an incidence of approximately 0 5 per cent having been recorded in large series The diagnosis of abscess is usually made because translucent areas are seen in radiographs taken during the phase of resolution some probably represent true cavities but they are not usually associated with much sputum and quickly disappear *Abscess formation is commonly seen in staphylococcal pneumonia* (Brock 1945) This condition, particularly when the staphylococcal invasion accompanies influenza virus infection is often rapidly fatal without clinical or radiological evidence of abscess formation. When the disease is less overwhelming and its course is prolonged, the sputum gradually increases in amount and single or multiple abscess cavities appear in the lungs Brock has pointed out that these are characteristically empty or almost empty of liquid and present a thin walled soap-bubble appearance The sputum which at first gives an almost pure growth of *Staph aureus* later contains other organisms as well *The stage of abscess formation may continue chronically and the* bacterial flora is usually then indistinguishable from that of non specific pulmonary suppuration In other cases the inflammatory process subsides but when this occurs the large distension abscesses are often slow to disappear Occasionally they persist and may be wrongly regarded as congenital cysts Staphylococcal pyæmia from a focus elsewhere in the body may produce abscess formation in the lungs These abscesses are typically small, multiple, and empty but the distinction from the abscess phase of staphylococcal pneumonia is frequently difficult. The treatment of both types is to avoid surgical *drainage and to give adequate dosage of penicillin*

Pneumonia due to Friedlander's bacillus is rare Collins and Kornblum (1929) regard the earliest stage as a lobular pneumonia the lobular areas coalesce and very massive consolidation results which is not limited by lobar boundaries Extensive destruction of the lung takes place in these areas with the production of abscess cavities. At this stage death almost always occurs Clinically after a sudden onset the patient becomes severely ill His sputum is tenacious has little odour and contains large numbers of the organisms His fever does not usually rise above 102° F and commonly he has few abnormal *signs in his chest Although in the past the mortality has been very* high it has been recognised for many years that the disease is not always fatal and may sometimes pursue a chronic suppurative course Pneumonia due to Friedlander's bacillus must be remembered when abscess formation occurs in areas of massive consolidation during acute pneumonia and also as a possible cause of chronic pulmonary suppuration The recognition of pneumonia due to this organism has

become extremely important since the introduction of streptomycin which is effective against it

Certain other specific infections produce suppuration in the lung Apart from pulmonary tuberculosis, which may be regarded as a specific pneumonia with abscess formation, the only one of real importance in this country is actinomycosis This may present as a chronic pneumonia with purulent sputum and multiple small pulmonary abscess cavities The diagnosis is usually difficult and often months elapse before the organism is demonstrated in sputum or perhaps more commonly in pus draining from chest wall sinuses The treatment is with doses of penicillin of the order of 4 to 8 million units a day, continued for a minimum of six weeks

Suppuration Associated with Bronchial Carcinoma Cases of pulmonary suppuration in relation to bronchial carcinoma form a very important group There are two main ways in which lung abscess may be caused by carcinoma The first is by breakdown of the growth itself According to Tudor Edwards (1946) it is commonly the squamous type of growth which breaks down in this way, and the abscess formed has a thick and often irregular wall The second way is by infection of the lung distal to the bronchial occlusion produced by the growth In Brock s (1948) series of 405 cases of lung abscess bronchial carcinoma was the cause in 56 an incidence of 13 8 per cent Fifty three of these 56 patients were over 45 years of age, and in the middle aged and elderly the possible presence of bronchial carcinoma in association with pulmonary suppuration must never be forgotton

Non Specific Suppurative Pneumonia *Besides these cases of* pulmonary suppuration associated with specific pneumonias and with bronchial carcinoma a large group remains in which inflammatory consolidation of the lung proceeds to suppuration but in which specific ætiological factors are not found These cases occupy the suppurative *localised aspiration pneumonia category of Scadding's* classification (see p 243) and the term non specific suppurative pneumonia may be used to describe them The most severe variety of this group is acute lung abscess Less severe varieties in which early cavitation is not seen are not uncommon in medical wards The *latter* are localised pneumonias which occur in patients in whom infected secretions are present in the respiratory tract and they cause a fairly severe illness with purulent sputum It is likely also that if these conditions are not vigorously treated some progress as chronic suppurative processes in much the same way as do lung abscesses

Pathogenesis The view that acute lung abscess is an aspiration pneumonia (infected atelectasis) in which suppuration occurs early and completely is based mainly on the work of Brock (Brock *et al* 1942 Brock *1947a b and c)* *With his co workers he showed that*

the common sites in which lung abscesses occur namely the posterior segments of the upper lobes and the apical segments of the lower lobes, are precisely those where iodised oil comes to rest when injected into the trachea of a subject in the horizontal position In sleep during and after anæsthesia or in coma the patient is usually horizontal and it is at these times that conditions are most favourable for the inhalation of infected material into the bronchi Lung abscesses commonly occur when infected material is present in the respiratory tract and their association with dental sepsis sinusitis quinsy and tonsillectomy supports the aspiration theory There seems equally good reason to regard the less severe non specific pneumonias as being of the aspiration type since they are usually associated with acute or chronic respiratory tract infections It seems therefore convenient and reasonable to take the view that there is a whole range of aspiration pneumonias of varying severity in which suppuration occurs One type presents as a solitary abscess cavity with little surrounding pneumonia another as a predominantly pneumonic process Once the solitary abscess has become complicated by surrounding suppurative changes in the lung its chronic progress is much the same as that of the type which is mainly pneumonic from the beginning Thus it is possible to distinguish a chronic phase of pulmonary suppuration which may be called chronic non specific suppurative pneumonia This term includes chronic lung abscess but is used in preference to it since the group comprises many cases which did not begin as abscesses and some in which abscesses may never have been recognised clinically or radiologically at any time

Bacteriology The organisms found in the sputum of patients with non specific suppurative pneumonia are commonly mixtures of the following types *Str viridans* non hæmolytic streptococci pharyngeal neisseriæ organisms of the hæmophilus group occasionally diphtheroids and sometimes small numbers of the higher types of pneumococcus hæmolytic streptococci and staphylococci There is however little doubt that anærobic organisms of the spirochætal group are responsible in certain cases for the production of lung abscess Such organisms are found around the teeth of persons suffering from pyorrhœa and pulmonary abscesses have been produced in laboratory animals with material scraped from such teeth These organisms are highly proteolytic and it seems likely that the most severe types of suppuration in which extensive abscess formation is an early feature are caused by anærobic organisms As an abscess develops it ruptures into neighbouring bronchi so producing conditions which must favour the growth of ærobic organisms Once this has occurred the anærobes must usually be overgrown but during the course of prolonged pulmonary suppuration local conditions in

the lung may from time to time encourage their growth At any rate, fœtid sputum, which is associated with the presence of anærobes, is found early in the course of some cases of lung abscess and occurs from time to time in most long continued pulmonary suppuration

Clinical Course The clinical features of acute lung abscess are well recognised and need not be described here The onset of the less severe varieties of non specific suppurative pneumonia with fever, cough, and sputum varies according to the severity of the infection and degree of suppuration produced The chronic course of non specific suppurative pneumonia (Logan and Nicholson 1949) is one of repeated febrile periods, each lasting usually a week or two Purulent sputum is coughed up from the onset and the febrile periods are often associated with a reduction in its amount Between attacks most patients are able to be up and about and often feel quite well The amount of sputum brought up daily is commonly between two and seven ounces and the majority of patients have blood streaked sputum at some time during the illness Clubbing of the fingers is almost always found, and physical examination usually reveals signs of con solidation which are rarely as extensive as might be expected from the radiological appearances White cell counts are seldom more than 12 000 per c mm

Radiological Features At the onset most cases have radiological evidence of segmental consolidation, whether or not it breaks down early to form an abscess In the chronic progression of the disease the radiological appearances vary The most usual course is that the disease spreads apparently directly into the surrounding lung This extension is not limited by interlobar septa In some cases spread occurs by the aspiration of material from the affected part of the lung into fresh segments Cavitation may occur at any stage of the disease It may occur early or late in the original lesion and may sometimes disappear The freshly invaded parts frequently cavitate and there may be multiple cavities of different sizes present in the same lobe or lung The radiological appearance often remains sta tionary for two or three months this being commonly associated with the periods of clinical improvement Sooner or later there is usually a further febrile attack and radiological evidence of spread of the disease Spread to the opposite side is often late in appearing or may not occur at all

In most cases there is at some time evidence of partial clearing of the pneumonic process When this occurs radiological evidence of fibrosis usually remains Extensive fibrosis may result from long continued suppuration and when this happens bronchograms show distortion of the bronchial tree and bronchiectasis Frequently also pulmonary cavities in communication with the distorted bronchi remain

Differential Diagnosis Some aspects of the differential diagnosis of suppurative pneumonia are of importance The recognition of the specific pneumonias in which suppuration occurs depends mainly on the isolation of the specific organisms in pure or almost pure culture from the sputum or on their recovery from the blood stream In the chronic phase of both staphylococcal pneumonia and that due to Friedlander s bacillus the specific organism is usually associated with others which have established themselves in the damaged lung In these circumstances it may be possible to guess the original nature of the infection by considering the clinical course of the disease but distinction from the non specific variety is not then very important because of the similar course and prognosis

Pulmonary tuberculosis because of its long course and rather similar radiological appearance may sometimes be confused with chronic suppurative pneumonia It is usually distinguished without difficulty First of all, suppurative pneumonia is commonly associated with sources of infected material in the respiratory tract Then the onset with the early production of a considerable and sometimes very large amount of purulent sputum is characteristic of suppurative pneumonia and quite unlike the early stages of pulmonary tuberculosis *Finally repeated examination of the sputum for tubercle bacilli with* negative results both by direct examination and by culture may be regarded as adequately distinguishing the suppurative process from tuberculosis

The distinction of non specific suppurative pneumonia from suppuration in association with bronchial carcinoma is most difficult Bronchoscopy must be carried out, and unless the patient is insufficiently co operative it is better done under local anæsthesia If the patient is febrile and has profuse sputum when first seen it is usually wise to wait until improvement and sputum reduction have occurred after a short period of treatment It is clear that when on bronchoscopy a biopsy specimen containing carcinomatous tissue is obtained no difficulty in diagnosis arises On the other hand when the suppurative process is of lobar extent and no growth is seen bronchoscopically it is *possible to give considerable weight to the negative finding* since an associated growth may be expected to involve the main lobar bronchus and therefore be visible In the case of lesions of segmental extent especially in the upper lobe a negative bronchoscopy is not of such significance since a carcinoma involving the segmental bronchus may be beyond bronchoscopic vision It is this sort of lesion which gives the greatest difficulty in differential diagnosis In the active phase of the disease bronchography is rarely of assistance since even where there is no carcinomatous obstruction the iodised oil is usually preven ted from entering the relevant bronchus by pus and pulmonary debris

In cases of doubt if other considerations allow it thoracotomy should be performed

Bronchiectasis complicated by consolidation of the lung around dilated and inflamed bronchi may be confused with chronic suppurative pneumonia The history will usually suggest the correct diagnosis The bronchiectatic patient will commonly have a long history of cough and sputum often going back into childhood, he will often have had pneumonic episodes in the past and the pneumonia with which he presents himself will usually clear fairly rapidly Although the two conditions can usually be distinguished it may sometimes be impossible to draw a sharp line between a suppurative process spreading from dilated and infected bronchi and one which involving alveoli in its development, produces bronchial distortion and dilatation In these circumstances, the practical importance of the distinction is not great

Treatment of Non-Specific Suppurative Pneumonia The less severe varieties if seen in their early stages are dealt with on the general lines set out for the aspiration pneumonias It is wise to *continue treatment until the radiological opacity has cleared and the* sputum ceased Nowadays, acute solitary abscess of the lung rarely needs to be drained surgically (Sutherland and Grant 1950) Almost always with a regime like that set out below for chronic suppurative pneumonia resolution without serious structural damage to the lung may be obtained If more than minimal bronchiectasis or fibrosis remains then the consideration of treatment is along the same lines as for the chronic disease

In chronic suppurative pneumonia treatment may be summarised as follows When the patient comes into hospital his sputum should be examined and cultured and the sensitivity of its organisms to antibiotics and the sulphonamides determined Meanwhile he should begin postural drainage and coughing under the care of a physiotherapist as soon as he is well enough he should spend four hours a day in a position suitable for drainage of the affected part and should, if he can sleep in this position at night The sputum in almost all cases contains large numbers of organisms sensitive to penicillin and this should be given in doses of two million units a day For the first six or seven days sulphamezathine should also be given After two or three weeks *it is well to re examine the sputum since it may* be found to contain organisms which are mainly penicillin resistant and one of the other antibiotics should be substituted In a matter of days the patient will be greatly improved symptomatically but the regime will usually need to be continued for a minimum of six weeks In the majority of cases it is possible to achieve a state in which there is very little but usually still purulent sputum a feeling of well being and radiographic evidence of fibrosis where there had previously been

consolidation and cavitation In some where the extent of the disease or other considerations clearly preclude pulmonary resection this may be regarded as an adequate result many of these will have further episodes of pulmonary infection and will need repeated courses of treatment In those patients where there are no such clear contra indications bronchograms should be carried out in order to determine which lobe or lobes are damaged and which are apparently intact Where the extent of the involvement as shown by the bronchograms does not preclude it resection of the affected pulmonary tissue must be undertaken

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PULMONARY INFILTRATIONS WITH EOSINOPHILIA

Since the publication of Loffler s paper in 1932 there has been considerable interest in the association of eosinophilia in the blood with pulmonary infiltration The recognition of this association is to some extent arbitrary since pulmonary infiltration is not clearly defined and means usually no more than a shadow in the radiograph of the lung *which may or may not be associated with symptoms and signs* Also in certain patients similar episodes are not always associated with eosinophilia Nevertheless the idea that cases presenting this association might be usefully considered together was put forward at a meeting of the Thoracic Society in 1950 by Livingstone and his colleagues who suggested that such cases might be grouped under the term pulmonary eosinophilia The conditions included are Loffler s syndrome prolonged pulmonary eosinophilia tropical eosinophilia pulmonary eosinophilia with asthma and polyarteritis nodosa with pulmonary infiltrations

Loffler's syndrome (Loffler, 1945 is probably the best general account) has been described in many parts of the world The symptoms are mild or may be non existent Usually there is a slight fever, with a little cough and occasionally a trace of sputum Often there are no abnormal physical signs in the chest but radiographs show mottled or confluent shadows These may vary a good deal in extent and may clear in one place to reappear elsewhere They disappear in a matter of days—usually less than 12 As the radiological shadows begin to clear there is a rise in the eosinophils in the blood The total white cell count is commonly a high normal with an eosinophilia which may be as high as 50 per cent, but is more often under 20 per cent The eosinophilia may last longer than the pulmonary changes In some patients presenting this syndrome *Ascaris lumbricoides* infestation has been found, and it is thought likely that in them the condition is a manifestation of hypersensitivity to this worm However, the idea that Loffler's syndrome is a transient allergic response has been widely accepted in some cases it may be due to worm infestation, in others the allergen may not be discovered

Individual cases have been described in which a condition in most respects like Loffler's syndrome instead of clearing up in a week or two lasts for several months The eosinophilia may be rather higher than in the transient variety In most cases of this prolonged pulmonary eosinophilia recovery is complete but relapses occur In some allergens have been identified and in others it has been suggested that brucella infection or the taking of sulphonamides was responsible

In tropical eosinophilia (Weingarten 1943 Soysa 1949) the symptoms are commonly bronchitic in type associated sometimes with asthmatic attacks and often with bronchial spasm and wheezing It is a chronic condition and may last several months or years Radiographically widespread fine mottling of both lung fields is the commonest finding The white cell count is almost always more than 15 000 per c mm with an eosinophilia of 20 to 90 per cent In most cases complete relief of symptoms and radiological clearing result from the giving of organic arsenicals either intravenously or by mouth In some cases mainly from Ceylon mites have been isolated from the sputum, and mite infestation of the respiratory tract has been suggested as causing the condition

In asthmatic patients the occurrence of aspiration pneumonias is not uncommon Usually these are not associated with eosinophilia In some asthmatic patients the association of pulmonary infiltration with eosinophilia suggests an allergic rather than an infective origin for the pulmonary consolidation (Harkavy 1941) In most of these the condition is an incident during chronic or recurrent asthma but some patients are free from asthma except during the existence of the

pulmonary infiltration The symptoms are usually cough and sputum which may contain eosinophils and there is often some fever which is sometimes recurrent The radiographic shadows are usually localised and vary greatly in extent from one case to another They may dis appear and recur in different parts of the same or opposite lung The eosinophilia is mostly of the same order as that found in tropical eosinophilia In some instances the condition clears up in a month or two and the patient returns to his asthmatic course in others the attacks recur over many years Occasionally when a specific allergen can be identified desensitisation may be a successful line of treatment Antihistaminics may also be tried In general however the treatment of this form of pulmonary infiltration is as unsuccessful as the treatment of asthma itself

In some cases of polyarteritis nodosa the association of pulmonary infiltration and eosinophilia has been recorded Asthma also occurred either during the final illness or as a pre existent condition in about half of these It may be that such cases represent a link between polyarteritis nodosa and the rest of the group in which eosinophilia is associated with infiltration of the lung The view put forward by Livingstone and his colleagues was that all these conditions represent hypersensitivity reactions to various stimuli When the reaction is brief and apparently confined to alveoli Loffler s syndrome results When it is longer but still alveolar in type it is termed prolonged pulmonary eosinophilia In tropical eosinophilia and in pulmonary eosinophilia with asthma the bronchi also are involved whereas in polyarteritis nodosa the disturbance is primarily vascular

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the final answer to which awaits isolation and study of the virus of encephalitis lethargica

It must be borne in mind however, that the Parkinsonian syndrome *is primarily* the symptom complex of damage to the corpus striatum, that pathological evidence suggests that it can arise as a result of lesions at various levels of the striatum and that the syndrome occurs under a variety of clinical circumstances including physical trauma manganese poisoning and syphilis Although in some such instances the provocation of latent virus infection is certainly possible, the attribution of all cases of the Parkinsonian syndrome to the unidentified virus of encephalitis lethargica would postulate a distribution as wide spread almost as that of the organism of herpes simplex, and appears unduly speculative

Classification With the qualifications implied above a clinical classification of the Parkinsonian syndrome embraces the following types —

Idiopathic paralysis agitans has a modal age of onset in the sixth decade, and is usually characterised by right sided tremor rather than rigidity as the presenting symptom with inconspicuous ocular signs and without mental changes In few cases is there any evidence of significant arteriopathy and there is neither clinical nor pathological justification for the practice especially frequent in the American literature, of describing this condition as "arteriosclerotic Parkinsonism

Post encephalitic Parkinsonism begins usually before the age of 40 Rigidity is usually a more prominent feature lateralisation is less pronounced, and most cases exhibit ocular symptoms many excessive salivation and a greasy skin and some oculogyric crises and mental changes

Indeterminate Parkinsonism may occur at any age above 20 but cases now tend to be more frequent over 40 and present a variable picture somewhere between the two types outlined above

In the writer s view *Arteriosclerotic Parkinsonism* first clearly defined by Critchley (1929) is a distinct and far from uncommon clinical entity Its characteristic features are that it usually has a rather abrupt onset late in life, and a step like as opposed to an insidious progression that it is never unilateral and that the tremor is coarser approximating more to the senile type Bulbar features such as dysphagia dysarthria and emotionalism are common arteriosclerotic dementia and focal vascular lesions outside the extrapyramidal system often ensue and there is peripheral and retinal evidence of arterial degeneration, usually without hypertension

Whether or not *Syphilitic Parkinsonism* has a separate existence is uncertain That a Parkinsonian syndrome may complicate tabes

dorsalis is well known but there is no unanimity as to whether this results from syphilitic mesencephalitis or from the occasional coincidence of two not very uncommon diseases

Traumatic Parkinsonism is also a subject of contention Non progressive Parkinsonism can certainly follow severe head injury when it is probably due to hæmorrhage in the region of the corpus striatum Parkinsonian symptoms are also often part of the picture of progressive traumatic encephalopathy (punch drunk) where they are usually associated with ataxia dementia and dysarthria Finally there is no doubt that progressive symptoms of Parkinsonism may first become evident following head injuries of no great severity, and that in some such instances the evidence suggests at least exacerbation if not provocation of the disease The evidence for provocation by general injury is less substantial but the condition has followed *electrocution*

Toxic Parkinsonism has resulted from exposure to nitrous oxide carbon monoxide carbon disulphide manganese potassium cyanide and barbiturates

Juvenile Parkinsonism is very rare indeed and it is not certainly known whether it represents a true (heredofamilial) entity or an unusually early post encephalitic condition

Finally Parkinsonian symptoms occasionally occur when the corpus striatum is the seat of *primary or secondary neoplasm* and they may be present as a component part of the clinical picture of *Jakob Creutzfeldt s disease* (with spasticity and pre senile dementia) and Kinnier Wilson s *progressive lenticular degeneration*

Surgical Treatment Whatever the ætiology the treatment of Parkinsonism is palliative and symptomatic and this applies no less to surgical than to medical measures

During the past 15 years a variety of surgical operations have been devised for the treatment of extrapyramidal involuntary movements and since the grave disadvantages of de afferentation of the limb preclude the clinical use of division of the appropriate posterior roots which is otherwise effective in reducing such movements operative interference has aimed chiefly at interruption of the main motor pathway through which the tremor is mediated Amongst such operations are anterolateral spinal tractotomy at cervical levels (Putnam 1940 Oliver 1950) or in the mid brain (Guiot and Pecker 1949) transventricular division of the anterior limb of the internal capsule sometimes with extirpation of the caudate nucleus (Meyers 1942 Browder 1948) and removal of varying areas and amounts of motor and pre motor cortex alone (Bucy and Case 1937 Bucy 1940 Klemme 1940) or combined with spinal tractotomy (Scott 1944)

The limitations of such surgery are obvious The first is that the operations are directed solely to the relief of tremor which often takes

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It must be borne in mind however that the Parkinsonian syndrome is primarily the symptom complex of damage to the corpus striatum, that pathological evidence suggests that it can arise as a result of lesions at various levels of the striatum and that the syndrome occurs under a variety of clinical circumstances including physical trauma, manganese poisoning and syphilis Although in some such instances the provocation of latent virus infection is certainly possible the attribution of all cases of the Parkinsonian syndrome to the unidentified virus of encephalitis lethargica would postulate a distribution as wide spread almost as that of the organism of herpes simplex, and appears unduly speculative

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Post encephalitic Parkinsonism begins usually before the age of 40 Rigidity is usually a more prominent feature lateralisation is less pronounced and most cases exhibit ocular symptoms many excessive salivation and a greasy skin, and some oculogyric crises and mental changes

Indeterminate Parkinsonism may occur at any age above 20 but cases now tend to be more frequent over 40 and present a variable picture somewhere between the two types outlined above

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than is physically possible Even slight symptomatic improvement accompanied by the knowledge that a new method of treatment is being used may thus sometimes produce dramatic if short lived improvement

These observations not only indicate the difficulty of objective assessment of new remedies They also emphasise the necessity in practice of accompanying any drug regime by psychotherapeutic measures if reassurance encouragement and an attempt to keep the patient employed in some physically unexacting and inconspicuous job merit the term

In the last resort assessment of results depends on the subjective response of the patient Probably the nearest approach to clinical objectivity is the observation of the patient s family as to his performance of personal and household duties

In view of these difficulties it is therefore not surprising that the therapeutic history of the disease presents a melancholy chronicle of transient enthusiasms Since the introduction of hyoscine by Charcot in the eighties great claims have been made for Bulgarian belladonna massive atropine dosage bulbocapnine and curare and since these have all failed to achieve unanimous acceptance or sustained adoption scepticism as to the newer remedies is natural

Current Therapy There can be little doubt that drugs of the atropine group remain the sheet anchor of medical treatment and form the basis of therapy in most cases Some cases are of course so mild that no treatment is required but in most patients *hyoscine hydrobromide* 1/200th to 1/50th of a grain three times a day or *tincture of stramonium* in doses of from 10 to 75 minims three times a day will do much to decrease rigidity though less to reduce tremor *High atropine dosage* has perhaps fewer advocates than formerly though it is undoubtedly valuable in severe cases The dosage is gradually built up from 0 5 mgms (1/120th grain) in a drachm of water by similar daily increments to a maximum of 10 mgms (1/6th grain) or more in divided doses British Drug Houses supply tablets containing 1 0 mgms (1/60th grain) and 4 0 mgms (1/15th grain) for this purpose

At the higher levels of dosage with any of these drugs *pilocarpine nitrate* 1/6th grain once or twice a day may be necessary to control dryness of the mouth while a daily drop of 1/4 per cent *eserine* solution into each eye will minimise the risk of glaucoma in the older patient and diminish the troublesome dimness of vision This however sometimes demands special glasses to correct the difficulty in accommodation

Amphetamine sulphate or *dextro amphetamine sulphate* (*Dexedrine*) in the usual dosage of 10 mgms or more twice daily often helps to control associated depression and retardation and is also the most

second place to rigidity as the patient's main source of disability Secondly operative measures are applicable only to the small minority of younger patients who are chiefly disabled by tremor strictly *unilateral in distribution, limited in extent, and unaccompanied by other evidence* of progressive disease Such patients probably comprise not more than five per cent of all cases and are not conspicuous among those who *insistently* demand surgical treatment Thirdly, the tremor is relieved always at the expense of adding a greater or lesser degree of pyramidal spasticity to the plastic rigidity of the affected part In the case of cortical operations the risks of severe hemiparesis or focal epilepsy are real

It must be admitted that spasticity appears to be considerably less than would be expected particularly in the case of antero lateral tractotomy even where as for example by Oliver (1950) the lateral column of the cord is *completely sectioned by a deep incision* and although operations on the cortex or basal ganglia seem hardly applicable to Parkinsonism (though the former are certainly justifiable in the *grossly incapacitating movements of severe athetosis*), it *seems* possible that tractotomy may have a place in the treatment of a small group of cases By and large however, it is difficult to feel despite the importunity of patients and the pertinacity of surgeons that the disease offers a very profitable field for surgery

Drug Treatment Unfortunately medical treatment also leaves much to be desired despite recent enthusiasms It is always difficult accurately to assess the value of symptomatic treatment in a chronic incurable disease, and this difficulty is nowhere more evident than in Parkinsonism Even in the case of orthodox treatment with atropine and its analogues the effect of drugs varies strikingly in cases apparently *similar clinically some such patients claiming very much greater* benefit from one member of the group than from any other In the case of the newer synthetic drugs this variability of response is very *much more pronounced The time honoured observation that many* patients with severe Parkinsonism can execute rapid emergency movements with agility when rigidity renders ordinary movements *slow and difficult* is another indication of the *lability of symptoms* and emotional factors are equally striking in their influence on the state of the disability Again patients will often claim considerable benefit from a drug the objective effect of which is not at all apparent to an experienced observer while particularly in the case of some of the newer drugs it is a common observation that after striking improvement for weeks or months the patient may slip back into his previous condition the drug apparently losing its effect Probably one factor in the variability of results is that muscular activity is so great and effort for the Parkinsonian patient that often he normally does less

intravenously reduces the rigidity and tremor of Parkinsonism transitorily without atropine like effects but oral administration (Berger and Schwartz 1948) is still experimental and its results less predictable while acute respiratory paralysis is a risk attendant on heavy dosage

Artane (*Trihexyphenidyl*) a synthetic antispasmodic of American origin with side effects similar to but on the whole less severe than those of the atropine alkaloids has won more general favour than any of the above preparations The dosage is from 1 mgm twice daily to 10 to 40 mgms daily in divided doses Careful studies (Doshay and Constable 1949 Corbin, 1949) have shown that although headache and mental confusion may occasionally accompany its administration it is usually well tolerated and apparently devoid of serious danger It requires less meticulous adjustment of dosage than the other drugs and improves at least a third of all cases treated while it tends also to have a favourable effect on the patients psychological state

The latest drug to be introduced is *Lysivane* (*N (2 diethylamino n-propyl) phenothiazine hydrochloride*) (Palmer and Gallagher 1950) a member of the same group of drugs as *Diparcol* This drug has not yet been extensively tested in England but it is claimed to be more effective and less toxic than its precursor The drug is supplied in tablets of 0 05 gr and is given in amounts up to 0 5 gr daily or even more Judgment as to its toxicity must be reserved until it has been more widely used

In summary this profusion of therapeutic agents is of itself a poor omen for their individual efficacy At the time of writing hyoscine and its analogues possibly in association with amphetamine or *Benadryl* is probably the safest and most effective routine with *Artane* as a useful alternative The other drugs have not yet proved their superiority and should be reserved for trial in severe and obstinate cases In any patient changes of drug routine from time to time will help and constant encouragement to maintain physical activity is an essential of any regime Energetic physiotherapy is often dramatic in its immediate results even in the severest cases and together with the intensive administration of belladonna is the secret of one much publicised continental treatment It is unfortunately one of the most expensive forms of persuasive psychotherapy and it is hardly practicable to continue it throughout the course of so chronic a malady

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effective drug in the control of oculogyric crises The clinical improvement which sometimes attends the taking of antihistamine drugs such as *Benadryl* in full dosage (50 mgms three or four times daily) is so dramatic and the drugs are of such low toxicity that this method of treatment is always worth trying as a supplementary measure It is not known whether the action of this group of drugs is due to their atropine like effects, or to the experimentally demonstrated choroidal and cerebral congestion which follows their administration (Budnitz 1948 Ryan and Wood 1949) If *Benadryl* or its analogues produce troublesome drowsiness this may be diminished by the coincident administration of *Amphetamine* or by substituting the new anti histaminic *Thephorin* (Roche) which is mildly euphoriant

The newest drugs for use in Parkinsonism however, are intended to act as substitutes for rather than supplements to the atropine group, and it should be emphasised immediately that the latter drugs particularly in large dosage should never be abandoned abruptly any change over should be gradual to avoid withdrawal symptoms which may otherwise prove severe

The drugs which have attracted most attention include '*Diparcol*' *Parpanit* *Myanesin* *Artane* and *Lysivane*

Diparcol (*B diethylaminoethyl N phenthiazine hydrochloride*) (Duff 1949) is a French drug related to the anti histamines given in doses gradually increasing from 0 05 gm three times daily to 0 25 gm six times daily The incidence of side effects is high Nausea vomiting mental confusion depression drowsiness and paræsthesiæ may occur early in treatment Agranulocytosis has been reported low white cell counts are common and there have been cases of sudden death on withdrawal of the drug, which should always be gradual Since *Diparcol* benefits only a minority of patients even in the hands of those who have used it extensively it would appear unlikely to find a permanent place in the treatment of Parkinsonism

Much the same applies in the writer s view to *Parpanit* (*diethyl amino ethyl l phenylcyclopentane l carboxylate*) (Schwab and Leigh 1949) There is no doubt that this Swiss drug closely related to *Trasentin* materially reduces rigidity in some patients and produces objective electromyographic improvement The usual dosage is 0 0125 gm three hourly gradually increasing to 0 2 to 0 4 gm daily Toxic effects are commoner but less serious than with *Diparcol* Over 60 per cent of cases develop undesirable side effects in which giddiness and nausea are prominent sometimes with a feeling of lightness in the limbs while in 20 per cent of patients the drug is entirely ineffective Both these drugs require exceptional care in the adjustment of dosage and in general supervision

Myanesin (*mephenesin or 3—ortho toloxy—1, 2—propanediol*)

obtained under good conditions and with careful control can usually be relied upon but negative tracings are of much more uncertain significance and leave the clinician dependent either on other methods of diagnosis or entirely on clinical assessment Above all it should be stressed that *even repeatedly normal resting records do not exclude epilepsy*

In general it can be said that electroencephalographic records of normal subjects are individually variable and largely dependent on inborn factors as is shown by the similar patterns found in identical twins The normal ten per second alpha rhythm which has its chief origin in symmetrical areas of the occipito parietal cortex indicates a state of physiological rest in this part of the brain and is abolished by visual or mental activity or sensory stimulation It shows a gradual increase in rate from six per second in infancy to between 8 and 13 per second in adolescence and maturity Conditions of depressed physiological activity such as sleep surgical anæsthesia or severe cerebral anoxia lead to the appearance of slow waves often of high voltage and frequently grouped Increased cortical activity on the other hand is accompanied by a reduction in alpha rhythm and the appearance of faster activity

Clinical use of the E E G still depends mainly on visual interpretation of the tracings and although unanimity of opinion as to the exact significance of some changes has not yet been reached the value of the method is established particularly in the localisation of intracranial space occupying lesions the assessment of cerebral trauma and its sequelæ and the investigation of patients with suspected epilepsy

Intracranial Lesions The use of the electroencephalogram in locating intracranial space-occupying lesions depends not on the nature of the lesion itself which is electrically inactive but on the disturbances which it produces in surrounding brain tissue The abnormal slow delta waves (less than one to three per second) which are often found in the vicinity of a tumour arise in brain tissue damaged by pressure œdema or anoxia and are the most characteristic electroencephalographic signature of a space occupying lesion of any kind directly or indirectly involving the cerebral cortex Patient electroencephalographic exploration of such cases by Walter (1936) led to the demonstration that in some cases such a lesion could be circumscribed with accuracy by the findings of *phase reversal* (mirror image tracings) in records obtained from electrodes placed on either side of the point of propagation, Although phase reversal cannot invariably be demonstrated it remains the theoretical ideal and the most unequivocal E E G evidence of such a lesion In some cases however a persistent focal maximum intensity of slow activity without phase reversal or even consistent asymmetry of alpha rhythm may be of

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CLINICAL APPLICATIONS OF ELECTROENCEPHALOGRAPHY

Since the first edition of this book the electroencephalogram has established itself firmly as an important ancillary aid to neurological diagnosis There have been technical improvements in the instrument itself, more refined mathematical methods of analysing the complex superimposed rhythms of the tracings have been developed and sensory stimuli have been increasingly employed to evoke latent abnormalities, but there have been relatively few developments of major importance in the clinical use of the method More general employment of the electroencephalogram has raised its own problems and it should be stressed again that the records are of value only when they are expertly interpreted by an observer also in possession of, and able to assess the full medical history of the case It must be appreciated that the tracing lacks the static quality of the average electro cardiogram, and presents a picture of electrical activity in the brain at a particular time and under particular circumstances In fact, the record varies from day to day, and if important decisions depend on it repeated tracings should be obtained Consistently positive findings

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and not merely in localisation minimal E.E G changes in the presence of clear clinical or radiological evidence of a superficially situated tumour favour a benign lesion Thirdly the recent development of the electrocorticogram (an E E G obtained directly from the brain exposed at operation) has provided a valuable source of information as to the extent and operability of cerebral lesions the limits of which may not be macroscopically evident

Head Injury and Traumatic Epilepsy Since the electroencephalographic results of such a relatively well controlled form of brain injury as that inflicted by prefrontal leucotomy are widely variable, it is not surprising to find considerable variability in the records obtained after accidental injury The commonest finding is a general abnormal slow discharge with suppression of the alpha rhythm and often with associated paroxysmal rapid discharges (Williams 1941) As the effects of concussion wear off these changes tend to become localised at the site of trauma and sometimes in areas remote from this (contre coup etc) The degree and persistence of the electrical changes show some positive correlation with the severity of the injury as assessed by the duration of unconsciousness and the absence of electroencephalographic abnormalities in a record taken within a few days of injury is substantial evidence against significant cerebral damage During recovery the changes become less marked and the record may become normal the alpha rhythm at first being slower than usual, but gradually returning to its previous frequency In some cases however abnormalities may remain after the resolution of symptoms and particularly in young subjects they may be permanent, while about half the patients with persisting post contusional symptoms show abnormal discharges which may be of some value in management and prognosis Heppenstall and Hill (1943) have shown in such cases that abnormal waves of focal origin are probably due to the injury but that generalised abnormalities are equivocal since they may well be of constitutional origin A poorly regulated alpha rhythm for example cannot be accepted as medico legal proof of a preceding brain injury for it may well have been present before the accident In any case generalised post traumatic changes tend to regress and the E E G s of patients who had mild head injuries two years previously show an incidence of abnormality not materially different from that found in the unselected population

Subdural, and sometimes epidural hæmatomas may give rise to various changes in the E E G The commonest finding is a general diminution in electrical activity over the area covered by the hæmatoma wh ch may be chiefly due to the increased distance between the electrodes and the cortex There are again various complicating factors and comparison with a recording made after the injury but

value in localisation while in frontal tumours bilateral electrical abnormality may indicate involvement of the *corpus callosum*

As already stated all such changes depend not on the nature of the lesion itself, but on the degree of secondary cerebral dysfunction, and are therefore of value only in conjunction with the clinical features of the case and the results of other investigations Benign meningiomata or deep seated gliomata may be associated with a discharge approximating to the physiological 'alpha" rhythm, whereas the changes are most dramatic in malignant tumour or abscess The reliability of the method was confirmed by Williams and Gibbs (1939) and the claim of Yeager *et al* (1940) that successful localisation is possible in as many as 80 per cent of cases has been fully confirmed Failure is chiefly in cerebellar tumours where the method is of little value except for occasional suggestive findings in the occipital regions in children, and in benign midline superficial (e g parasagittal) meningiomata and acoustic tumours where E E G changes may be minimal Pituitary tumours and aneurysms also rarely provoke electrical activity of diagnostic value In basal and other deep seated tumours the interpretation of tracings is more difficult than with lesions near the surface, but the demonstration by Walter and Dovey (1944) of four to seven per second ' theta waves of considerable amplitude has proved of value Such waves probably arise from lesions near the thalamus or at any rate in the vicinity of the third ventricle and indicate a deeply situated lesion Sometimes they occur in association with 'delta' activity and in some such instances serial tracings may permit electroencephalographic differentiation between a superficial lesion extending deeply and a more deeply situated tumour spreading towards the surface

In some patients focal abnormalities may be masked by generalised slow activity associated with raised intracranial pressure Williams (1939) has shown that since these appearances may be dissipated and local changes revealed by dehydration but not by lumbar puncture they are probably due to œdema rather than to the pressure itself In occasional cases also false E E G localising signs may be produced by focal cortical œdema distant from the lesion or by the secondary pressure of a dilated ventricle

The chief practical value of the E E G in the localisation and diagnosis of intracranial space occupying lesions is first as a preliminary searching method involving no risk or inconvenience to the out patient with suspicious symptoms but no clinical or radiological signs of tumour In some patients for example with featureless headaches fits or abnormal behaviour of recent onset the E E G may reveal a lesion arising in one of the silent areas of the brain Secondly the electro encephalogram may on occasion yield information of value in diagnosis

The characteristic E E G pattern of *Grand Mal* is a crescendo of runs of fast spikes usually at a frequency of about 22 per second The motor and sensory clinical manifestations of grand mal are characteristically *unorganised* and the electrical abnormality usually symmetrical and diffuse It may however be focal in origin while a similar rhythm may even occur as a local phenomenon without further spread Some such cases of focal spike activity have been shown to arise in a cortical scar which probably resulted from birth injury

Clinically the term *Petit Mal* originally indicated any brief epileptic episode and the characteristic electrical activity found in such cases was described by Gibbs Davis and Lennox (1935) as the three per second wave and spike rhythm It is now clear however that such activity is found in only a minority of clinical cases of minor epilepsy *and that it is also seen in association with many akinetic falling* attacks and some cases of myoclonus while the E E G in many clinical cases of petit mal shows paroxysmal fast activity which indicates that the attacks represent from the E E G point of view brief episodes of major epilepsy

Wave and spike activity is symmetrical and synchronous over the whole cortex It is most commonly seen in the immature brain of childhood probably arises in the thalamus and is pathognomonic of idiopathic as opposed to symptomatic epilepsy It is certainly not found in lesions acquired after the first few months of life though there is evidence to suggest that it may occasionally follow injury at or near the time of birth It has one other important feature which may well have been responsible for the initial overemphasis on the clinical importance of this pattern it tends to be a more constant resting feature of the record than the fast paroxysms of grand mal and it is therefore proportionately more often seen in the inter seizure E E G

The term *Psychomotor Epilepsy* has taken the place of epileptic equivalent and is now applied to a wide variety of transient states of altered consciousness with *organised* abnormal activity and followed by amnesia Such cases are not always easy to recognise clinically and the conduct to which they give rise may be of great clinical and medico legal importance ranging from that of the difficult child to the violent criminal The characteristic E E G finding is flat topped four per second waves interspersed with irregular fast activity the two sometimes running together to produce a saw tooth appear ance This wave pattern has been shown to result from the organised linkage of waves of different frequencies chiefly in the three to ten per second band and often arising in the anterior part of the left temporal lobe gross lesions of which have long been known to be associated with behaviour disorders

before the onset of clinical signs of delayed bleeding is of more positive value than a single tracing, though it is rarely possible

Traumatic epilepsy presents a special problem which Williams (1944a) has studied by serial E E G s The early paroxysmal discharges noted above are not of prognostic significance in this connection but *in some cases, following the resolution of generalised changes* episodic discharges may arise from the site of or remote from, the injured area These are due to irreversible secondary changes and may increase in frequency and intensity to culminate in a clinical fit The inter seizure record is, however the source of electroencephalographic evidence as to the nature of fits occurring after head injury and its interpretation is not always easy Probably 75 to 80 per cent of post traumatic epileptics show E E G abnormalities and when these are both *focal* and *paroxysmal* their significance is usually clear In such cases also *focal* fast activity whether or not it is associated with post traumatic slow waves, is highly suggestive whereas symmetrical *generalised* fast activity is more likely to result from pre existing idiopathic epilepsy The most difficult problem however is presented when fits follow head injury in the absence of E E G abnormalities or in the presence of focal slow activity only Such activity is presumptive evidence of structural brain damage, but unless the nature and march of the convulsion support its origin in the region of the E E G abnormality the electroencephalographic diagnosis of traumatic epilepsy cannot be certain

Epilepsy Although electroencephalographic abnormalities in the epileptic subject were described by Berger in 1932 and epilepsy remains today the most practically useful field of application of the E E G its employment as an instrument of research has clarified our understanding of some aspects of the condition only to raise a host of *entirely new problems*

Epileptic seizures are always accompanied and usually preceded by abnormal cortical discharges In the case of petit mal recent evidence suggests these may prove to be a reflection of disordered action in a regulator of cortical activity situated in the thalamus Electrical activity in the cortex of the dog is practically abolished by division of thalamo cortical connections while epileptic cortical patterns of petit mal have been reproduced by direct thalamic stimulation in the experimental animal and there is recent evidence also that such rhythms arise initially from the thalamus in man There is, however no evidence to suggest a thalamic origin for the dysrhythmia of major epilepsy

Gibbs, Gibbs and Lennox (1943) have described three main E E G patterns of epileptic cortical activity the clinical significance of which has been somewhat *clarified by more extensive clinical experience*

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Epileptic seizures are always accompanied and usually preceded by abnormal cortical discharges In the case of petit mal recent evidence suggests these may prove to be a reflection of disordered action in a regulator of cortical activity situated in the thalamus Electrical activity in the cortex of the dog is practically abolished by division of thalamo cortical connections while epileptic cortical patterns of petit mal have been reproduced by direct thalamic stimulation in the experimental animal and there is recent evidence also that such rhythms arise initially from the thalamus in man There is however no evidence to suggest a thalamic origin for the dysrhythmia of major epilepsy

Gibbs, Gibbs and Lennox (1943) have described three main E E G patterns of epileptic cortical activity the clinical significance of which has been somewhat clarified by more extensive clinical experience

per cent of aggressive psychopaths and are sometimes indistinguishable from those of idiopathic epilepsy (Hill and Watterson 1942 Hill 1944) The medico legal importance of these findings is apparent and electroencephalographic evidence of disordered cerebral function has been accepted in courts of law

Moore (1945) has described a convincing series of patients in whom *paroxysmal abdominal pain was associated with* abnormal E E G discharges chiefly frontal in origin These cases responded to anti convulsant drugs and appear to confirm Kinnier Wilson s clinical conjecture of abdominal epilepsy.

Findings in *migraine* are of questionable significance and little clinical value *Narcoleptic* attacks yield a record similar to that seen in normal sleep The suggestion of a constitutional cerebral factor *predisposing to loss of consciousness in syncope* (vascular fainting) receives some support from the incidence of low voltage fast activity amongst habitual fainters

Indications for Electro encephalography The practical value of the E E G in epilepsy is fourfold First *in the elucidation of obscure attacks* of disturbance of consciousness a resting E E G showing either paroxysmal abnormalities or specific larval attacks provides strong confirmation of an epileptic origin but since about 25 per cent of epileptic subjects yield normal tracings a negative result does not exclude epilepsy In such cases diagnosis must be based on the total picture Secondly in epilepsy first appearing in adult life, particularly with Jacksonian attacks or convulsions with local onset the E E G may help to answer the question—*are the patients fits idiopathic or due to structural disease?* A brain tumour producing recent fits as a presenting symptom is on the whole likely to be superficially situated and to produce persisting focal abnormalities in the E E G while the presence of wave and spike activity paroxysmal fast discharges a bilaterally symmetrical record or a specific response to over breathing render idiopathic epilepsy more probable Thirdly electroencephalo graphic studies of the families of epileptics indicate the value of the method in *avoiding the transmission of epilepsy* to the succeeding generation If the epileptic patient marries a subject with a normal E E G his chances of producing epileptic offspring are greatly reduced

Finally particularly since the introduction of new anti convulsant drugs the E E G is of considerable value in *the choice and control of treatment*

Treatment of Epilepsy While it remains true that most patients with epilepsy can be correctly diagnosed and efficiently treated without recourse to electroencephalography an E E G always adds some information to the assessment of a case and there are instances in which this information is a prerequisite of successful therapy the

The electrical changes in idiopathic epilepsy may originate locally or they may be apparently generalised from the start In between clinical attacks about 75 per cent of epileptics show E E G abnormalities in a single record as opposed to 12 per cent of normal controls (Williams, 1944b) Some such records show only non specific abnormalities like those often found in neurosis psychosis, or unstable psychopathy others well defined paroxysmal activity of clear diagnostic value In a few patients larval electroencephalographic seizures are accompanied clinically by momentary intellectual blunting In most cases, however, the abnormalities seen are less specific than is suggested by the description of the wave forms described above and indicate epileptic activity in general rather than diagnostic entities The record may show more than one type of epileptic activity in a patient with only one kind of seizure the patient with wave and spike activity on the resting record may suffer only from major fits, or the patient with fast paroxysms only from clinical petit mal and the frequency and severity of attacks is in no way proportional to the degree of electrical abnormality seen Young epileptics show the highest incidence of resting E E G abnormalities, and these may be brought out, particularly in petit mal by over breathing or such physiological changes as shutting the eyes Increasing frequency and intensity of dysrhythmia over hours or days may presage a clinical seizure, and seizures are particularly liable to occur under circumstance where there is a physiological change in cortical electrical activity, as in falling asleep, waking or emotion The basis of the clinical seizure in cortical dysrhythmia is evident in their relationship in time and also in partial continuous epilepsy and myoclonic attacks, where the cortical discharge is also synchronous with muscular contractions

The observations of Lennox Gibbs and Gibbs (1939 1940) that 60 per cent of relatives of epileptics as opposed to ten per cent of controls without such a family history showed abnormal tracings are of first importance Paroxysmal cerebral dysrhythmia appears to be the basis of idiopathic epilepsy itself genetically determined and possibly inherited as a dominant characteristic Probably only about one in 25 dysrhythmic subjects actually suffers from clinical epilepsy but the condition indicates a functional instability of the nervous system often associated with a lowered threshold to convulsions under the influence of such precipitating factors as head injury pregnancy and other toxæmias ether inhalation or brain tumour

Allied Disorders As well as confirming the epileptic nature of clinical psychic equivalents the E E G has clearly demonstrated the close relation to epilepsy of the less stereotyped conduct disorders seen in some psychopathic personalities Delinquency itself is unassociated with E E G abnormality but the tracings are abnormal in 65

cases the drug may be withdrawn after several months treatment without recurrence of attacks

A patient in whom major and minor attacks are associated will probably do best on phenobarbitone and tridione it is of course more important to control the former the onset of which may be provoked or exacerbated by tridione alone Status epilepticus which may ensue on the sudden cessation of any effective routine of treatment and sometimes follows the occasional severe convulsion which many patients experience on epanutin given without phenobarbitone is *probably best treated with intramuscular paraldehyde* Five to ten ccs can be repeated if necessary and paraldehyde is generally considered more effective than similar injection of soluble phenobarbitone (3 grains)

The E E G in other conditions All processes involving destruction of brain tissue may be characterised in the active stage by abnormal slow (delta) activity in the E E G often patchy in distribution and frequently replaced by a normal pattern when degeneration is complete Neurosyphilis with or without paretic signs encephalitis of various forms vascular lesions and some organic dementias are among the conditions in which such changes may be found

In general the application of electroencephalography to psychiatric disorders has yielded disappointing results Many studies have been carried out in the classical psychoses the neuroses and in mental deficiency without revealing convincing evidence of pathognomic abnormalities Non specific abnormalities are approximately twice as common in psychoneurotic patients as in unselected subjects and least common in highly selected groups such as bomber pilots Of the constitutional psychoses schizophrenia yields the highest proportion of abnormal tracings patients in the manic depressive group few There appears nothing inherently improbable in a correlation between E E G pattern and personality type but such evidence as is yet *available is equivocal*

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value of several of the newer anti convulsant drugs depends on the electroencephalographic and not on the clinical pattern of the seizure

Major epilepsy is best treated with either the barbiturates or the hydantoinates or with both in combination *Phenobarbitone* is sedative as well as anti convulsant, and acts by a general depression of cerebral activity, whereas sodium diphenylhydantoinate (Dilantin or *Epanutin*) inhibits epileptic activity without sedative or depressant effects Most American neurologists use the hydantoinates initially and the barbiturates as supplementary treatment The latter, however are rarely toxic whereas in the case of the former an effective dose may be only slightly below the toxic level In Britain it is therefore commoner to begin treatment with phenobarbitone and to add epanutin if necessary The patient is usually started on ½ grain of phenobarbitone night and morning In the case of purely nocturnal major epilepsy there is evidence in favour of the greater efficacy of nightly epanutin barbiturates may increase the tendency to convulsions by deepening sleep The dose of phenobarbitone can be increased to 1½ grains twice daily and well beyond this in many patients particularly in severe cases under institutional conditions Sleepiness is sometimes less pronounced with *phemitone* (1½ to 3 grains three times daily) than with phenobarbitone, or it may be diminished by giving five to ten milligrams of *amphetamine* twice daily Many mild epileptics are controlled by phenobarbitone or phemitone alone

If epanutin is given together with phenobarbitone an effective dose of each must be taken as their anti convulsant action is not of the same nature Epanutin is useful in major epilepsy sometimes effective in psychomotor attacks and of no value in petit mal, in which its administration may indeed increase the frequency of attacks The usual dosage is 1½ grains (0 1 grams) to 3 grains (0 2 grams) three times daily Careful supervision of treatment is necessary throughout and especially in the early weeks, to detect toxic effects (muscular inco ordination ataxia and nystagmus overactivity gastric discomfort erythemata hirsuties and hyperplasia of the gums)

Methyl phenyl ethyl hydantoin (*Mesontoin*) in similar dosage is possibly less toxic

Tridione (trimethyl oxazolidine) is a non sedative drug which is a convulsant in animals its often dramatically beneficial effect is apparently limited to those cases of petit mal in which the E E G shows wave and spike activity The usual dosage is 0 3 grams two or three times daily but this can be doubled The occasional occurrence of agranulocytosis as a result of tridione therapy demands close supervision on the usual lines advice to the patient about possible toxic symptoms is probably a more effective safeguard than the regular white cell counts which are medico legally advisable In many

cases the drug may be withdrawn after several months treatment without recurrence of attacks

A patient in whom major and minor attacks are associated will probably do best on phenobarbitone and tridione it is of course more important to control the former, the onset of which may be provoked or exacerbated by tridione alone Status epilepticus which may ensue on the sudden cessation of any effective routine of treatment and sometimes follows the occasional severe convulsion which many patients experience on epanutin given without phenobarbitone is probably best treated with intramuscular paraldehyde Five to ten ccs can be repeated if necessary and paraldehyde is generally considered more effective than similar injection of soluble phenobarbitone (3 grains)

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CEREBRAL ANGIOGRAPHY

Although cerebral angiography (arteriography and phlebography) was first carried out by Egas Moniz in 1927 the wide extension of the use of this method from the demonstration of cerebral circulation in cases of intracranial aneurysm or angiomatous malformations to its employment in the investigations of a much wider variety of cerebral lesions awaited the introduction of the percutaneous method 20 years later (Lindgren 1947)

Liquid diodone (perabrodil diodrast) is now the medium most widely used and the usual method employed is the injection of a 35 per cent or 50 per cent solution of the contrast medium (ten ccs for each view) into the common or internal carotid artery with the neck extended The usual carotid arteriogram therefore involves four such injections in order to obtain lateral and antero posterior views on each side If vertebral angiograms are also carried out to demonstrate deformities of the basilar and vertebral arteries and their branches (sometimes through a catheter inserted in the radial artery) the number of injections is greater but serious complications are rare even in cases with raised intracranial pressure



FIG [illegible]4 Aneurysm of internal carotid artery in the cavernous sinus

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Fig. [illegible] Normal lateral angiogram showing anterior cerebral (A) and Sylvian (B) arteries



FIG 25 Large temporo occipital angioma supplied by hypertrophied vertebral artery



Fig. 23 Parietal meningioma outlined in the later arterial phase

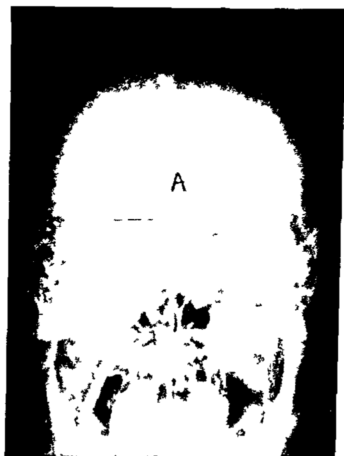


FIG 27 Normal antero posterior angiogram showing anterior cerebral (A) and Sylvian (B) arteries



Fig. 28 Parietal meningioma outlined in the later arterial phase

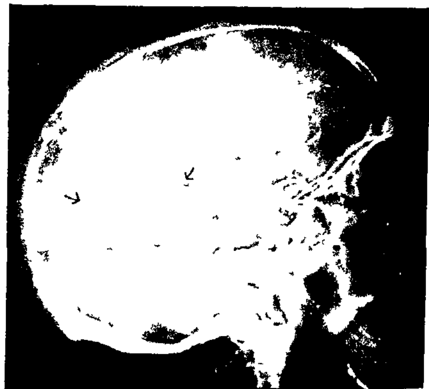


Fig 29 Large malignant temporo occipital glioma with pathological vessels indicated by arrows

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The most essential requisite of success is the adequate radiological equipment and team work necessary to obtain immediate pictures (arteriograms) and the exposures two and four seconds later which demonstrate respectively the superficial veins and the large veins and sinuses (first and second phase phlebograms) Still more elaborate equipment is necessary for the rapid serial angiography described by Curtis (1949) and for this reason angiography is at present less used in most general hospitals than air encephalography being chiefly employed in neurosurgical clinics Where adequate facilities are available however it has the great advantage over the latter method that it can be performed on out patients

The injection is followed by a burning pain behind the eye, flushing and dilatation of the pupil Complications are rare but include a slight rise of temperature urticaria (thorotrast is still used in cases of known sensitivity to iodine) head pains local hæmatoma or thrombosis puncture of the internal jugular vein transient spasm of cerebral arteries sometimes producing hemiparesis and cervical sympathetic paralysis The mortality in most series is in the neighbourhood of one per cent

Among the general observations of interest which have resulted from the many hundreds of angiograms which have been made, particularly in the Scandinavian countries are the great rapidity of the cerebral circulation which is four or five times as fast as that through the vessels of the scalp and the normally autonomous distribution of the main cerebral arteries The circulation of each hemisphere seems to be almost entirely independent and the communicating arteries and anastomoses across the mid line appear to have little function under normal conditions

The method has now been applied in intracranial diseases of every type although its most unique value is still in the demonstration of aneurysms (Fig 24) and vascular tumours and malformations (Fig 25) It has shown for example that a certain number of cases of spontaneous subarachnoid hæmorrhage are due not to the anticipated congenital aneurysm but to small cerebral angiomata The greatest value of the method in cases of suspected tumour is where air-encephalography cannot be carried out because of raised intracranial pressure, or where ventriculography can demonstrate but cannot localise a unilateral expanding lesion The site of the tumour is usually best shown by the displacement of neighbouring arteries which it produces In lateral and anteroposterior views the Sylvian group (middle cerebral) and the supra callosal arteries (anterior cerebral) are clearly seen the former being superficial and the latter deep (Figs 26 and 27) Anatomical considerations will show how displacement of these vessels may serve to localise a space occupying lesion in the hemisphere in many cases with

considerable accuracy In some instances however the angiogram may demonstrate the tumour more directly and may assist in the elucidation of its type as well as its situation A meningioma may show not only considerable increase in the calibre of the supplying arteries which arise typically from the external carotid but also a characteristic diffuse vascular " blush " (Fig 28) Malignant gliomas and metastases may show patchy accumulation of contrast medium and the formation of abnormal vessels in the tumour area (Fig 29) whereas a slowly developing tumour such as an astrocytoma is often seen as an abnormally avascular area displacing the larger vessels This is the appearance usually shown by brain abscess cyst, or hæmatoma in any situation

Air encephalography surpasses angiography in the demonstration of hydrocephalus In gross congenital hydrocephalus the arteriogram reveals a few vessels splayed out over the brain and appearing to radiate from a central point at the base Unilateral hydrocephalus tends to show upward displacement of the Sylvian group and upward and forward dislocation of the anterior cerebral arteries but these changes may be slight even when the hydrocephalus is clearly evident in air pictures

Obstruction of the lumen of a major cerebral artery by thrombosis or hæmorrhage can of course be directly visualised and in gross cases of atheroma even the irregularities in the calibre of the vessels may be seen

Internal Carotid Artery Thrombosis One interesting and not uncommon condition which has been clarified by angiography is thrombosis of the internal carotid artery (Wolfe 1948 Ameli and Ashby 1949 James 1949) This condition is commoner in the adult male and much more frequent on the left side thus involving the major hemisphere The thrombosis occurs most commonly just above the bifurcation of the common carotid though it may arise in the intracranial course of the internal carotid artery The clinical picture is one of episodic hemiparetic attacks involving the arm more than the leg and often with dysphasia recurring over a period varying from hours to years but most commonly of some months and terminating in a severe hemiplegia of similar distribution This is occasionally accompanied by hemianopia but the ophthalmic artery usually escapes and the contralateral blindness of classical carotid hemiplegia is rarely seen Angiography reveals the block in the artery and injection of the opposite side may show the circulation spreading across the midline

The ætiology is obscure Occasional traumatic and syphilitic cases have been known for many years but they are rare Thrombo-angiitis obliterans polyarteritis nodosa and temporal arteritis may cause the lesion but most often it appears to arise on the basis of local

atheroma which is not uncommon at this site even in younger subjects Familial cases have been recorded suggesting the possibility of some local structural factor

Papillœdema occurs occasionally differentiation from cerebral tumour may be difficult and definitive diagnosis is impossible without angiography

Partial recovery is common Neither cervical sympathectomy nor peri arterial stripping have proved themselves in treatment and excision of the affected segment of the artery has little value In an otherwise healthy patient without evidence of diffuse arteriopathy the use of anti coagulants would appear rational

Surgical treatment of Spontaneous Subarachnoid Hæmorrhage Increasing employment of angiography has also led to renewed interest in the surgical approach to spontaneous subarachnoid hæmorrhage usually due to a leaking congenital aneurysm on the circle of Willis or an adjacent artery

Recent reviews (Hamby 1948 Hyland 1950) have shown that with conservative treatment about half of all cases die in the initial attack and that of the 20 per cent of survivors who suffer a subsequent hæmorrhage usually within a few weeks of the first about two thirds succumb A considerable proportion of all survivors are more or less disabled and probably not more than one in four of all patients makes a complete recovery Surgical treatment has been carried out occasionally for nearly 20 years but until recently its general application was limited by the impossibility of localising or even lateralising the lesion in the majority of cases

Falconer (1950) however reports the results of surgical treatment in 40 consecutive cases with a 65 per cent satisfactory recovery rate and only 12 5 per cent mortality despite the fact that nearly two thirds of these cases had already developed recurrent bleeding

The surgical routine usually carried out is carotid angiography on both sides followed by ligation of the appropriate common carotid artery Wechsler and Gross (1948) have shown that angiography even in the presence of continuing hæmorrhage carries little risk and this should be carried out in cases with deepening unconsciousness or increasing signs Some workers carry out the procedure immediately in all cases but others prefer to wait for a few weeks until the condition is gradually improving In view of the number of patients who suffer a second hæmorrhage during this period immediate angiography offers an obvious advantage There appears to be little doubt that common carotid ligation is less dangerous than tying the internal carotid which has in itself a mortality between 20 per cent and 30 per cent when carried out in the presence of continuing subarachnoid bleeding Falconer ties the common carotid artery in two stages completing a

partial occlusion by tying the silk ligature tightly two or three days after the initial operation

In some instances circulation through the internal carotid artery becomes re established by a retrograde flow down the external carotid, demanding subsequent ligature of the former These steps alone appear to deal satisfactorily with some aneurysms, particularly those *arising on the intracranial course of the artery below the circle of Willis* but not infrequently the aneurysm may refill through a collateral supply from the opposite side

Most aneurysms causing subarachnoid hæmorrhage are situated on the anterior part of the circle of Willis and following ligation Falconer favours a direct surgical approach by means of a frontal craniotomy The ideal operation is occlusion of the artery above and below the aneurysm, but where this is impossible hammered muscle may be wrapped round it (Dott 1933) or the anterior cerebral may be occluded proximal to the aneurysm

Wechsler and Gross (1948) also use common carotid ligature, and mention the combination of this method with deep radiation in the smaller group of cases due to vascular malformations rather than aneurysms

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POLIOMYELITIS

Since the epidemic of 1947 acute anterior poliomyelitis has become one of the most important communicable diseases in this country and

is the subject of intensive experimental investigation and epidemiological study bedside observation has greatly increased our understanding of the natural history of the disease and has brought to light important clinical features hitherto unrecognised

Pathogenesis and Epidemiology There is still doubt as to the usual route by which the poliomyelitis virus reaches the human nervous system In the rhesus monkey experimental studies have established the nasopharyngeal route as the common one and histological changes accompany the spread of the virus from the olfactory bulbs via the thalamic region to the spinal cord In man however histological changes in the olfactory bulbs are rare (Robertson 1940 Faber and Silverberg 1946) and here as in the chimpanzee involvement of the nuclei of the fifth ninth and tenth cranial nerves and of sympathetic ganglia suggests that the route of infection is either from the oropharynx to the medulla or from the intestine to the spinal cord In fatal human cases the virus can be demonstrated in the walls and secretions of pharynx and intestine and in mesenteric lymph nodes and abdominal viscera while in the nervous system it has a predilection *for the ganglion cells of the cervical and lumbar enlargements of the* spinal cord the vestibular and cerebellar nuclei and the motor cortex. Howe and Bodian (1942) have demonstrated the strict neurotropism of the virus and have traced and measured its centripetal spread from its peripheral point of entry to the nerve filament along the axoplasm *of peripheral nerves and across synapses and along axons to the* susceptible parts of the neuraxis Bodian (1948) has shown that such infection of the central nervous system often occurs during the first day of fever The occurrence of epidemics of bulbar poliomyelitis following tonsillectomy (Aycock 1942) and in association with ton*sillitis (Scott Brown 1931) suggests that trauma and possibly bacterial* infection may open up peripheral neural pathways to invasion by the virus Suggestive evidence in this direction is provided also by Gard s (1944) demonstration that in healthy mice carrying the virus of mouse poliomyelitis (Theiler s disease) paralysis may be provoked by inter*current gastro intestinal infections*

The possibility that in man poliomyelitis is predominantly an alimentary infection receives further support from the higher attack rate in rural and suburban communities and from the seasonal incidence of the disease which with its peak in late summer and autumn is more like that seen in the enteric group than in diseases known to be spread by droplet infection The very wide distribution of the virus in epidemics is also consonant with this view Present in pharyngeal secretions only during the acute phase of the disease it can be demonstrated in the stools of patients contacts convalescent subjects and healthy carriers, some of whom may later develop the

partial occlusion by tying the silk ligature tightly two or three days after the initial operation

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POLIOMYELITIS

Since the epidemic of 1947 acute anterior poliomyelitis has become one of the most important communicable diseases in this country and

In summary these observations show that while exertion during the few days preceding the onset of symptoms is irrelevant in relation to the subsequent course of the disease physical exertion during the 48 hours following the onset of symptoms is clearly correlated with the occurrence of moderate or severe paralysis which is rare in patients confined to bed from the outset No such relationship applies to cases of bulbar poliomyelitis while evidence as to the role of local muscular fatigue in localising paralysis remains suggestive but not entirely satisfying possibly because of the complexity of most muscular movements

Confinement of the sporadically occurring case to bed from the onset of symptoms is obviously impracticable but during an epidemic it is imperative as far as possible and there can be no doubt that publicity should be given to such advice in every epidemic while a further practical measure would be the holding of school and similar athletic events as far as possible outside the poliomyelitis season

The preparalytic illness In view of the above observations and also to help in minimising epidemic spread the recognition of pre paralytic and nonparalytic cases is obviously of major importance Reliable studies depend on facilities for isolation of the virus and these were available to Casey *et al* (1948) who made a careful analysis of 64 proven subclinical cases Of these 24 had no symptoms whatever and these were nearly all under the age of six The commonest picture however was that of a mild febrile illness with headache con stipation and drowsiness sometimes with myalgia Running nose diarrhœa and cough were features neither of these subclinical cases nor of a comparable group of clinical cases which later developed a more recognisable illness characterised by neck stiffness The latter cases however did show an appreciable incidence of sore red throat and leg pains Whether the occurrence of sore throat in clinical cases is due to a larger quantity of virus in the throat is uncertain in some instances a preceding bacterial infection lowering local resistance might be a factor

Bulbar Poliomyelitis Brain stem poliomyelitis usually occurs in association with the commoner spinal type of the disease but spinal paralysis may sometimes be inconspicuous and occasionally absent The understanding and management of the condition are important because it accounts for most deaths from the disease because of its clinical complexity and because skilled assessment and therapy are of undoubted value in lowering its high mortality The importance of this is that if the patient can be tided over five to ten days of desperate illness the bulbar paralysis tends to recover with little or no residual disability

The explanation of the profound dyspnœa seen in severe cases of bulbar poliomyelitis is by no means simple Involvement of the *upper*

disease It has also been identified in water food and dust and in sewage, flies and mice

Nevertheless although occasional explosive milk borne epidemics have been described and food and water borne infection remains a clear possibility, epidemiological observations have clearly shown that human infection usually spreads radially by case to case contact and that the pharynx is almost certainly the portal of entry All the evidence indicates that infectivity is greatest in the febrile preparalytic stage and in a similarly brief invasive phase in the carrier Contact infection is masked by the fact that in any epidemic only a small proportion of those infected develop paralysis Whether infection occurs primarily by inhalation or by ingestion remains a matter of conjecture most observers favour the former view

Clinical Features Amongst clinical contributions of major importance are recent studies of preparalytic and bulbar poliomyelitis and of the relation of paralysis to physical activity and preceding inoculation

Paralytic poliomyelitis after immunisation Recent observations have indicated that when poliomyelitis is prevalent a number of children develop the paralytic form of the disease within a month of prophylactic inoculation and that in many of these cases the distribution of the paralysis is atypical with a predilection for the injected limb (McCloskey 1950 Martin 1950 Hill and Knowelden 1950) The occurrence is probably commoner with intramuscular than with subcutaneous injections and with locally irritating solutions but it seems less likely to be due to anything specific in the substance given or to syringe infection than to local trauma This is particularly so since *a similar occurrence has been observed after injection of penicillin and* indeed after forms of trauma not involving injection at all It seems clear also that inoculation more than a month previously has no effect in what would appear to be the conversion of silent to paralytic poliomyelitic infection

From a practical point of view it would appear wise to abandon prophylactic inoculation entirely at times when poliomyelitis is prevalent the evidence is sufficiently convincing to justify this step without awaiting the results of the extensive field survey demanded by some public health authorities as a prelude to such action

Physical activity and paralysis That physical fatigue like body chilling or warm weather predisposes to the onset of paralysis in infected patients has long been suspected and has recently been proved in the experimental animal The recognition however of a frequent quantitative relationship between exertion during the preparalytic phase and the severity of subsequent paralysis is due entirely to the acute clinical observations of Ritchie Russell (1947 1949) which have since been confirmed by Horstmann (1950)

ological study by virus neutralisation tests and probably account for second paralytic episodes in occasional patients, and for some second attacks of the disease the demonstration that cross infection can and does occasionally occur in the hospital ward and the recognition that pregnant women are particularly susceptible to the paralytic form of the disease which tends to occur with unusual severity during the later months of pregnancy (Taylor and Simmons 1948)

Prophylaxis and Treatment During epidemics the infectivity of non paralytic and preparalytic cases must be borne in mind and early recognition of these with isolation during the febrile period is imperative The closing of swimming baths the avoidance of chilling and fatigue and the banning of tonsillectomy are advisable anti fly measures should be taken and fæcal contamination avoided Since *clinically recognisable cases constitute only a small fraction of infected* individuals in the community rigid isolation and quarantine are ineffective in preventing the spread of the disease

Although the theoretical basis of prophylactic passive immunisation of contacts is dubious and there is no clear evidence of its effectiveness a few authorities until recently recommended the intramuscular injection of 20 cubic centimetres of convalescent or pooled adult serum under these circumstances In the case of the established disease however both controlled clinical observations (Park 1932) and experimental studies have shown that convalescent serum given at any stage after infection fails to influence either mortality rate or severity of paralysis In any case recent developments lead to the conviction that any form of injection should be avoided during the course of the disease and that even in the case of contacts there is more chance that it will do harm than good

Active immunisation with virus attenuated by ultra violet irradiation (Milzer *et al* 1944) appears to be effective in protecting mice but is not yet applicable to man

The routine treatment of acute poliomyelitis remains a subject of doubt and controversy and the literature abounds with dogmatic claims uncritical enthusiasms and uncontrolled observations Where an attempt has been made to carry out controlled therapeutic tests the significance of the differences in end results between the more active and the more passive methods of treatment between those which employ early vigorous physiotherapy *and those which limit its use to* the convalescent phase and between those which employ a wide variety of spasmolytic drugs and those which rely on general sedation are unconvincing

Probably most cases of acute anterior poliomyelitis should be admitted to hospital if they are first seen in the acute stage In the preparalytic stage also definitive diagnosis usually demands lumbar

cranial nerves (5th, 7th and 8th) rarely causes anxiety but when the *lower cranial nuclei*, particularly glossopharyngeal and vagus, are affected dyspnœa and mortality increase The chief cause for this is pooling of secretion in the pharynx and larynx causing blockage of the airway with secondary anoxia which is sometimes evident in head ache confusional states and deepening stupor, and possible toxic effects from the accumulation of carbon dioxide Other factors are laryngeal spasm the aspiration of mucous plugs into the bronchi causing atelectases, and sometimes an apparently reflex pulmonary œdema

It is cases of this type which are most gratifying to treat and although treatment is complicated and exacting (e g Galloway and Seifert, 1949) its general principles are simple The most important rule is to *clear and maintain the airway and prevent anoxia,* and this is achieved by immediate efficient postural drainage preferably in the prone position and constant pharyngeal suction (the standard of nursing and the amount of such attention available are the most vital single factors in treatment) Here also curare may be of value in relaxing spasm atropine in reducing secretion and a sedative in allaying fear and restlessness When such measures are insufficient to free the airway intratracheal aspiration or bronchoscopic drainage may be more effective, but tracheotomy may be essential and the concensus of opinion seems to be that it could be performed more often with benefit Once the airway is established oxygen and an efficient respirator are valuable particularly in the severe tracheotomised case No food should be given orally until swallowing is restored nutrition and hydration being maintained by cautious parenteral fluids with a careful watch for pulmonary œdema

Two complicating factors may vitiate immediate and final results respectively Some cases of failure of regular respiratory rhythm are due to anoxia and are relieved by a good airway but in a minority they may persist and depend perhaps on direct damage by the disease to the respiratory centres Secondly complicating dyspnœa from intercostal paralysis of spinal origin though it responds well to the respirator is much slower to recover and may even prove permanent

In general, the terrifying nature of the bulbar disease to the patient should be borne in mind throughout and particularly when dealing with patients in the respirator It may not be necessary to take literally American advice to have a daily visitation by a psychiatrist to each of these cases but it is true that there is no greater test of patience, skill and the ability to inspire confidence on the part of doctor and nurse than is encountered in this condition

Other recent contributions of clinical importance have been the demonstration of multiple strains of virus which complicate epidemi

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and together with re-education of the effectors are stated to lead to recovery without deformity Paralysis due to the morbid anatomical changes in the anterior horn cells according to this view plays a relatively trivial part in the illness

As regards the treatment itself it must be agreed that acute polio myelitis is sometimes a painful disease and that muscle spasm may occur in the earlier stages It is true also that intensive and energetic physiotherapy sometimes produces striking improvement even in the presence of chronic disability However the absence of measures to prevent stretching of weakened muscles and repeated manipulations in the painful stages are difficult to justify while Kenny s interdiction of muscle testing during treatment renders adequate control of results impossible Much literature on the subject is unbalanced in its enthusiasm disregarding the natural history of the disease and in particular its tendency to spontaneous improvement while partisans of the method ignore the existence of non paralytic cases and deny the occurrence of residual deformities Excessive publicity has pre vented controlled observations by the alternate case method but the most careful objective attempts to assess the value of the treatment (Fairbank *et al* 1938 Ghormley *et al* 1944) have failed entirely to support Kenny s sweeping claims there is no evidence that the regime can completely or even significantly prevent paralysis or deformities and the results do not appear to differ materially from those obtained by other methods

The neuropathological concepts elaborated on the basis of Kenny s work are entirely speculative and unsupported by objective evidence Indeed electromyographic and chronaxic studies (Kohn *et al* 1945) have clearly shown that it is the flaccid muscles which show degenera tive electrical changes and that these are found in spastic muscle only when such spasm is accompanied by weakness due to a co-existing *destructive lesion of the lower motor neurone* These and similar studies suggest also that muscle spasm in poliomyelitis is the result of a hyper irritable stretch reflex which may play a protective role rather than or the dubious release phenomenon due to lesions of inter nuncial neurones suggested by theorists of the Kenny school These considera ions provide little justification for the administration of acetylcholine or prostigmine (Kabat and Knapp 1943) and even less for the hazards of curarisation (Ransohoff 1945) in the acute stage of the spinal form of the disease even if these drugs do relieve muscle pain and spasm

In conclusion it would appear that the controversy over the Kenny treatment has served a useful purpose in stimulating both physio therapeutic endeavour and attention to the psychological factor which is so important in all chronic disease within the framework of orthodox

puncture if only to exclude meningitis, though should the case be seen at a stage when the clinical diagnosis is clear it is almost certainly better for the patient to escape this procedure Reassurance, rest and sedation are probably the chief desiderata of treatment in the acute phase, with local heat and analgesic or spasmolytic drugs when pain or spasm demand them

In severe spinal cases the use of the respirator poses problems which are difficult both from the technical and the human points of view but in practice so long as occasional cases which have been treated in it are restored to reasonable health the use of the respirator can never be denied to any dyspnoeic patient A careful follow up study of patients so treated would be of real help in the making of more rational decisions as to the use of the method

The general use of splinting has rightly fallen into disrepute because it certainly encourages contractures but where there is partial foot drop or some similar localised flaccid paresis the use of a light night splint is a reasonable precaution against overstretching of weakened muscle

Reliable evidence as to the value of physiotherapy at any stage of the disease is extraordinarily hard to find but there seems little doubt that in the convalescent patient at any rate an energetic programme of such therapy helps in many ways to minimise his disability Its dreary prolongation over endless months of out patient attendance is, however to be deprecated as grossly uneconomic and of very question able value

The Kenny Treatment During the past decade an extensive American literature has accumulated on the subject of Sister Kenny's method of treatment of poliomyelitis Primarily an empirical physio therapeutic technique this is also the basis of new concepts of neuro muscular pathophysiology which are entirely at variance with existing views

The essentials of the Kenny treatment (Cole *et al* 1942 Pohl and Kenny 1943) are the immediate institution of passive movements and energetic muscle re education in the acute stage of the disease without massage electrotherapy or splinting The patient is kept flat in bed with the feet supported and pain and spasm are relieved by the frequently repeated applications of hot wet packs to limbs and trunk

The fullest exposition of the hypotheses which have been erected on the basis of this method is found in the book by Cole *et al* (1942) These workers consider muscle spasm more important than paralysis in the disease and attribute weakness of movements to spasm of the antagonists rather than to paralysis of the effector muscles which they describe as mentally alienated Hot packs release this spasm

and together with re education of the effectors are stated to lead to recovery without deformity Paralysis due to the morbid anatomical changes in the anterior horn cells according to this view plays a relatively trivial part in the illness

As regards the treatment itself it must be agreed that acute polio myelitis is sometimes a painful disease and that muscle spasm may occur in the earlier stages It is true also that intensive and energetic physiotherapy sometimes produces striking improvement even in the presence of chronic disability However the absence of measures to prevent stretching of weakened muscles and repeated manipulations in the painful stages are difficult to justify while Kenny s interdiction of muscle testing during treatment renders adequate control of results impossible Much literature on the subject is unbalanced in its enthusiasm disregarding the natural history of the disease and in particular its tendency to spontaneous improvement while partisans of the method ignore the existence of non paralytic cases and deny the occurrence of residual deformities Excessive publicity has pre vented controlled observations by the alternate case method but the most careful objective attempts to assess the value of the treatment (Fairbank *et al* 1938 Ghormley *et al* 1944) have failed entirely to support Kenny s sweeping claims there is no evidence that the regime can completely or even significantly prevent paralysis or deformities and the results do not appear to differ materially from those obtained by other methods

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In conclusion it would appear that the controversy over the Kenny treatment has served a useful purpose in stimulating both physio therapeutic endeavour and attention to the psychological factor which is so important in all chronic disease within the framework of orthodox

treatment It has shown also (Cobb 1943) that "new and empiric methods of treatment, backed by uncritical enthusiasm, may produce many cures, but much physiologic nonsense The treatment may be good, but the ex post facto rationalisations of the therapeutist are usually bad"

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MYASTHENIA GRAVIS

The characteristic symptoms of myasthenia gravis depend on a chemical abnormality at the myoneural junction the exact nature of which remains uncertain but in which the transmitting mechanism or acetyl choline cycle is involved The relief of symptoms and restoration of normal electrical reactions in affected muscles which follow administration of physostigmine or prostigmine probably depend on inhibition of the hydrolysing action of cholinesterase This inhibition permits the accumulation of effector acetyl choline at the myoneural junction *There is however no evidence that premature destruction* of acetyl choline by excess of esterase is the primary mechanism of the disease attempts to demonstrate such an excess locally in muscle or in the blood have met with no success

Myasthenia gravis shows some striking similarities to partial curarisation which is known to raise the threshold to acetyl choline at the motor end plate Common to both conditions are successive involvement of ocular facial, bulbar and limb musculature abnormal muscular fatiguability and corresponding electrical reactions absence of normal muscular fasciculation after injection of prostigmine clinical improvement following administration of eserine prostigmine and potassium and exacerbation by quinine There is however one striking difference between them in that the excitatory threshold of the motor end plate to acetyl choline is not raised in myasthenia as it is by curarisation On the contrary myasthenic muscle is exquisitely sensitive to acetyl choline reaching it by the bloodstream (Harvey *et al* 1941) This sensitivity is similar to that seen in recently denervated muscle and suggests that the basis of myasthenia may lie in physiological denervation produced by inadequate release of acetyl choline at the motor end plate of affected muscles Such a hypothesis with its emphasis on a local factor is certainly more compatible with the clinical features of the condition and particularly with its local incidence than a purely humoral explanation

That a humoral factor is involved however is shown by a considerable body of evidence In 1938 Walker demonstrated an important case in which the circulation in both arms was cut off by sphygmomanometer cuffs and movements of the forearms were carried out until they tired Release of the cuffs was followed by the rapid onset of left ptosis Wilson and Stoner (1944) have followed up this work demonstrating the frequent exacerbation of myasthenic symptoms by fatigue of remote muscles and claim to have demonstrated in the serum of untreated patients a chemical substance which inhibits neuromuscular transmission in the frog nerve muscle preparation The observation that this effect is not produced by the serum of patients under treatment indicates that as well as its known action in inhibiting

esterisation of acetyl choline prostigmine may also influence the production or neutralise the action of this curare like blocking substance The mode of action of this circulating factor is unknown, and the suggestion that it might be produced by the thymus gland as well as by fatigued myasthenic muscle remains purely speculative

Amongst clinical features of myasthenia gravis which are stressed in recent literature are its occasional spontaneous recovery or duration for periods of many years without deterioration, its exacerbation by emotional disturbance and by exposure to sunlight the tendency to sudden death even while symptoms are controlled by prostigmine the striking remissions which frequently occur during pregnancy, and the recognition of typical cases in infancy Wilson and Stoner (1944) record a transient myasthenic picture in the newborn infant of a mother with myasthenia gravis

Diagnosis The most useful diagnostic test in myasthenia gravis remains the relief of symptoms following subcutaneous injection of 1 5 milligrams of prostigmine with 1/100 grain (0 6 milligram) of atropine to counter the muscarine like side effects of the drug on heart and gastro intestinal tract Tether (1948) has recently shown that an even more striking test can be obtained by the intravenous injection during 60 seconds of a smaller dose of prostigmine (0 5 milligrams) which relieves myasthenic symptoms within seconds or minutes as against half an hour or so Such an intravenous dose can safely be given without atropine which is used only in the event of side effects uncommon in the actual myasthenic Schwab and Viets (1941) have introduced a refinement of the diagnostic test studying the swallow reflex before and after the injection by means of a barium swallow Retention of barium in the pharynx and pyriform fossæ is clear evidence of structural disease affecting the swallowing mechanism and the restoration of a normal swallow by prostigmine injection permits a firm diagnosis of myasthenia gravis

In occasional cases larger doses of prostigmine may be necessary to produce the specific effect, but there are few patients in whom the risk of intentional exacerbation by quinine or curare should be taken The slight response to prostigmine seen in bulbar palsy and other forms of muscular atrophy and dystrophy is never sufficiently dramatic to cause confusion

Treatment While the information is still lacking which will integrate what is known of humoral and local factors in the pathological physiology of the disease existing knowledge of chemical changes at the myoneural junction has led during the past few years to the development of increasingly effective methods of medical treatment

In most cases oral has replaced parenteral administration of prostigmine, and from one to four 15 milligram tablets may be given

four hourly or at intervals suitable to the patient's mode of life. On such dosage atropine gr 1/100 (0.6 milligram) may be required two or three times a day but myasthenic patients have a high tolerance to prostigmine and many of them do not need atropine. Ephedrine ½-grain (30 milligrams) thrice daily augments the action of prostigmine in some patients probably by increasing muscle tone and in others potassium chloride 60 to 90 grains (four to six grams) six times daily may also reinforce its effect by enhancing in some way the action of acetyl choline.

The provision of a hypodermic syringe and ampoules of prostigmine for the patient to keep by her as advised by Viets (1945) is a useful safeguard against the sudden attacks of respiratory failure which so often prove fatal. The myasthenic patient's complaint of acute respiratory distress must always be taken very seriously even when as often it is at first quite unaccompanied by objective change in pulse or colour. In crises or where there is great dysphagia injection must replace oral therapy: ordinarily 0.5 milligram parenterally is equivalent to 15 milligrams by mouth and by hourly injection or by the intravenous drip method as much as 30 milligrams can be given in the course of 24 hours. Overdosage in emergency may make matters worse by stimulating excessive secretion of pharyngeal mucus and saliva and this should be kept under control with atropine.

Several new cholinesterase inhibiting drugs have recently been introduced. They are still in the experimental stage and although initial reports of one of these in particular (tetraethylpyrophosphate) are very encouraging experience is not yet sufficient to justify their general adoption in place of prostigmine. The first of these drugs investigated was diisopropylfluorophosphate (DFP) (Comroe *et al* 1946). This drug certainly reduces plasma cholinesterase effectively but is clinically inferior to prostigmine in the control of myasthenic symptoms and has been abandoned because of toxicity. Hexæthyl tetraphosphate (Westerbertberg and Luros 1948) is also clinically disappointing but tetraethylpyrophosphate (Burgen *et al* 1948) in doses of 8 to 15 milligrams daily by mouth abolishes myasthenic symptoms in some subjects for a longer period of time than is usual with prostigmine and reduces prostigmine requirements materially in others. Its general use however presents difficulties. It is rapidly inactivated by water and must be kept in anhydrous solution until just before use; it tends like DFP to be inactivated by circulating prostigmine which should therefore not be given until at least an hour after the tetraethylpyrophosphate and it not only produces in an appreciable proportion of cases severe muscarine like effects but also occasionally profound bradycardia with depressed S T segments and low voltage T waves. Convulsions have also been reported while the margin

between therapeutically effective and toxic dosage is narrow, and over dosage may lead to the onset of severe general muscular weakness (Stone and Rider, 1949) Although most of the toxic symptoms respond to atropine their severity is such as to limit the use of the drug at present to the control under expert supervision of prostigmine resistant or very severe cases

It is not surprising also to find myasthenia gravis amongst the many diseases in which pituitary adrenocorticotrophic hormone (ACTH) has been given experimentally There is evidence that while it may exacerbate myasthenic symptoms during administration considerable clinical improvement sometimes follows and may last for some months (Soffer *et al*, 1948 Torda and Wolff 1949) but neither the theoretical implications nor the practical significance of this finding are as yet clear

Thymectomy Weigert described the association of myasthenia gravis and thymus tumour in 1901, and in 1912 Sauerbruch performed the first thymectomy for this disease In the large majority of adequately reported autopsied cases the thymus is abnormal The commonest finding is simple hypertrophy with epithelial hyperplasia and prominent lymphoid follicles In a smaller proportion an encapsulated simple tumour (thymoma) is found, and in exceptional instances a malignant thymic neoplasm has been recorded in association with myasthenia

Evidence for an endocrine function of the thymus gland is slender Perhaps the most significant finding is the frequency of thymus enlargement in thyrotoxicosis with which both myasthenia gravis and other forms of myopathy may be associated but neither this nor the variable and unsubstantiated claims put forward for the myasthenic effects of thymus extracts are sufficient to support any causal relation between the gland and the muscular weakness

Thymectomy remains at present an empirical and far from completely evaluated method of treatment The most recent reports are those of Harvey (1948) Keynes (1949) Viets (1950), and Eaton and Clagett (1950) Consideration of these and similar papers dealing with smaller series modifies to some extent the enthusiasm aroused by earlier reports and unfortunately does nothing to simplify the selection of suitable cases for surgical treatment Both Keynes and Viets record material improvement in between half and two thirds of operated cases and Harvey produces some clinical evidence that such a remission rate is unlikely to be fortuitous most prolonged remissions tending to occur early in the course of the disease Unfortunately the differences of detail between these authors render their results even more difficult to assess There is a striking absence of unanimity as to the influence on surgical results of the existence of thymic tumour

the duration of the disease or the age of the patient while post operative remission is sometimes so long delayed that its dependence on removal of the thymus has been questioned

Eaton and Clagett (1950) in a carefully controlled study based on over 300 cases seen at the Mayo Clinic are frankly sceptical as to the effect of thymectomy on myasthenic symptoms in their 86 patients treated surgically Despite a proportion of dramatically successful cases these workers suggest that the better results reported following surgical as compared with medical treatment depend primarily on the selection of cases for surgery They find that where this factor is controlled by using comparable groups of patients (excluding very old or ill subjects very mild cases and chronic patients in whom a stationary condition is well established on prostigmine) the remission rate after surgery (35 5 per cent) shows no statistically significant difference from the rate of similar spontaneous remission on medical treatment (28 5 per cent) Clinically their control group was fairly comparable with the surgical group being composed chiefly of patients who had declined thymectomy These workers no longer recommend thymectomy except in the presence of radiological evidence of thymic tumour and here it is advised in view of the danger of malignancy of the tumour rather than in the hope of control of myasthenia Using the radiological technique described by Good (1947) which includes careful screening and lateral as well as stereoscopic posteroanterior chest views they find that radiological diagnosis of thymic tumour is almost infallible a finding which is in conflict with British experience

The decision for or against surgery in the individual myasthenic patient is therefore extremely difficult and there is an increasing suspicion that the chance of improvement with operation is not sufficiently greater than that with medical treatment alone to justify routine operation even though the mortality in expert hands is no more than one in twenty Surgery is certainly not indicated in the very mild case in subjects who can maintain social efficiency on regular medication or in the patient with localised symptoms of long standing unresponsive to prostigmine which probably depend on secondary muscular atrophy and fibrosis It is worse than useless where it is most tempting—as a last resort in the desperately ill and deteriorating case At present the most reasonable case for surgery would appear to be the young patient with a short history continuing deterioration and severe symptoms not efficiently controlled by drugs Even here and despite dramatically successful results in some cases the result is in no way predictable

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NEUROSURGICAL RELIEF OF INTRACTABLE PAIN

Spinothalamic Tractotomy—Surgery of the Autonomic system—Prefrontal Leucotomy

Neurosurgical relief of intractable pain in which radical treatment of the cause is impossible has recently attracted much attention The principle of such treatment is surgical interruption of the conducting pathway between the site of the lesion and the sensory cortex The emphasis placed on prefrontal leucotomy particularly by American writers has overshadowed other measures directed to the relief of severe pain even though these are in many cases equally effective and have the advantage of involving no injury to the personality

The chief application of *division of peripheral nerves* is in the treatment of trigeminal neuralgia *Division of posterior roots* (posterior rhizotomy) is another well recognised procedure directed to the peripheral neurone On the whole the results of this operation tend to

be disappointing but it is useful for example in the brachial pain of Pancoast s (superior pulmonary sulcus) tumour and in severe and painful injuries to the brachial plexus

Spinothalamic Tractotomy (anterolateral chordotomy) efficiently performed is probably the most useful surgical approach to intractable somatic pain arising below the nipple line The incision must be deep and situated well above the decussation of the spinothalamic fibres carrying pain impulses from the painful area The latter fact renders the operation less successful in painful conditions of the upper extremities and of the chest particularly as analgesia rather than hypalgesia is necessary for the relief of pain and because there is frequently considerable post operative recession of the upper level of the analgesia Attempts have been made to overcome these difficulties by dividing the spinothalamic tract in the medulla and even in the mid brain The operation is of great technical difficulty at these levels and has an appreciable mortality particularly from respiratory failure while ataxia from damage to the cerebellar pathways fortunately usually *transitory may be a complication The main complications of opera*tion are loss of sphincter control, and motor weakness It is remarkable that almost complete transection of the anterolateral columns of the cord leads to so little motor difficulty and incontinence does not occur after unilateral tractotomy but it may be a troublesome complication after the bilateral division of the tracts which is usually demanded by inoperable abdominal cancer Tractotomy is certainly the treatment of choice in severe intractable pain in the lower extremities Inoperable cancer lightning pains of tabes dorsalis peripheral ischæmia, and some cases of phantom limb are amongst conditions successfully treated by this method The condition has also been used in painful chronic arthritis in the lower limbs but it would seem here to have a more limited application than purely orthopædic procedures such as arthrodesis As indicated above the unilateral operation is preferable but even in apparently unilateral pain in the trunk the subsequent appearance of pain on the opposite side not infrequently demands a two-stage bilateral operation

Autonomic Surgery Recognition that the autonomic nerves are accompanied by afferent fibres has led to the performance of sympathetic surgery for the relief of intractable visceral pain both in the chest and in the abdomen In severe angina pectoris unresponsive to medical treatment for example, removal of the upper three or four thoracic sympathetic ganglia is as effective as and less hazardous than posterior rhizotomy Presacral neurectomy for dysmenorrhœa is a fairly familiar example of the same principle and injection or removal of the cœliac or superior mesenteric ganglia may be of value in severe pain without any removable cause arising in kidney bowel, or pancreas

Vagotomy for intractable peptic ulcer acts of course by division of efferent rather than afferent fibres but splanchnicectomy has also been used for the relief of severe pain in the occasional case where a peptic ulcer is inaccessible to radical surgical treatment because of cardio vascular or other contra indications to major surgery It is also claimed that post herpetic neuralgia is sometimes relieved by cervical sympathectomy

The most dramatic successes of sympathectomy however are in the treatment of causalgia following partial injury to the median nerve and here this is undoubtedly the treatment of choice

Prefrontal Leucotomy Although the treatment of intractable pain by prefrontal leucotomy has received wide publicity it should be borne in mind that it is a last resort The unilateral operation (Scarff 1949) produces less damage to the personality than when it is done on both sides and even when personality changes do ensue they may be not entirely without benefit to the patient in minimising the affective disturbance which accompanies his symptoms Even where the pain itself is not removed the patient tends to bear it with indifference it has been said that the pain remains but the suffering has gone Prefrontal leucotomy is probably the only surgical approach for example to incurable pain in the head and neck which has resisted division of the trigeminal and glossopharyngeal nerves by a posterior approach but even this operation cannot be guaranteed to remove all pains Thalamic pain and post herpetic neuralgia have sometimes proved resistant even to this form of treatment

These measures are certainly worth serious consideration in cases of very severe pain where the cause is untreatable and where the physician can be reasonably certain that complicating psychiatric factors are not a major cause of the patient s disability The greatest successes of such surgical treatment have undoubtedly been in the treatment of incurable malignant disease In other conditions the danger of personality changes must be given serious consideration as also must the possibility of recurrence of pain which is present in relation to all the measures described above These are still in the experimental stage and while it is reasonable that surgeons working in this field should apply them widely in order to assess their uses and limitations it seems questionable whether for example the surgical treatment of pain arising from secondary deposits of cancer in the liver is a justifiable measure The danger of morphine addiction in such cases has been much stressed, but the drug is useful not only because it relieves pain but for its effect in clouding consciousness and it is open to doubt whether it is not a lesser evil than further surgical procedures in a patient who has not long to live



Fig 30 Toxoplasmosis A serologically confirmed case in a two year old child with microcephaly choroido retinitis intracerebral calcification and a history of jaundice at birth

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TOXOPLASMOSIS

Protozoa of the genus *Toxoplasma* have been known for many years but that they can cause disease in man was recognised only in 1937 Toxoplasmosis is a generalised infection with a tendency to persist in the central nervous system The organism may be found in the body fluids and exudates of infected cases and is widely distributed intracellularly throughout the tissues The majority of the 40 cases on record have occurred in America or on the European continent but the first English case was reported in 1948 (Jacoby and Sagorin) Most cases result from intrauterine infection but the disease occurs also in older children and adults (Zuelzer 1944)

The mode of entry of the parasite is unknown but familial cases occur and there is some clinical evidence that contact with mammalian carriers leads to infection either directly or by way of an insect vector the parasite being widely distributed in small animals and birds The sequence of pathological events appears to be a focal necrotic vasculitis probably due to an antigen antibody reaction followed by granuloma formation and ultimately by calcification which may be seen on a skull X ray as dots or curvilinear shadows (Fig 80)

In congenital cases this process may be already far advanced at birth with gross encephalopathy accompanied by either hydrocephalus or microcephaly Such cases usually succumb early after an illness characterised by emaciation fever opisthotonus choroidoretinitis and often jaundice and hæmorrhages The disease is much rarer in older children in whom it may give rise to convulsions hydrocephalus a clear cut bilateral central choroidoretinitis with consecutive optic atrophy and an increase of cells and protein in the spinal fluid sometimes to the extent of xanthochromia Hepatosplenomegaly lymphadenopathy and anæmia may occur

Cases may simulate cerebral tumour while visual impairment and intellectual retardation may ensue in survivors In adolescence and

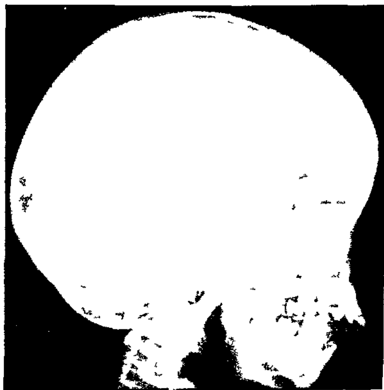


FIG 30 Toxoplasmosis A serologically confirmed case in a two year old child with microcephaly choroido retinitis intracerebral calcification and a history of jaundice at birth

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In congenital cases this process may be already far advanced at birth, with gross encephalopathy accompanied by either hydrocephalus or microcephaly. Such cases usually succumb early after an illness characterised by emaciation, fever, opisthotonus, chorioidoretinitis and often jaundice and hæmorrhages. The disease is much rarer in older children, in whom it may give rise to convulsions, hydrocephalus, a circumscribed bilateral central chorioidoretinitis with consecutive optic atrophy, and an increase of cells and protein in the spinal fluid, sometimes to the extent of xanthochromia. Hepatosplenomegaly, lymphadenopathy and anæmia may occur.

Cases may simulate cerebral tumour, while visual impairment and intellectual retardation may ensue in survivors. In adolescence and



Fig 30 Toxoplasmosis A serologically confirmed case in a two year old child with microcephaly choroido retinitis intracerebral calcification and a history of jaundice at birth

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Proliferation of organisms is suppressed, but they tend to form pseudo cysts and relapse is therefore not uncommon Amongst drugs tried without effect are penicillin streptomycin aureomycin, chloramphenicol (chloromycetin) paludrin and PAS In advanced subacute and chronic cases with severe hydrocephalus and choroidoretinitis treatment is of questionable value In the absence of any drug which will clearly destroy the parasites desensitisation with toxoplasma antigen is under trial (Frenkel 1949)

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ACUTE PORPHYRIA

Acute porphyria is discussed in this chapter because its major symptoms are so often neurological The term has replaced hæmatoporphyrinuria hæmatoporphyrin is not found in nature and the presence of uroporphyrin coproporphyrin and other abnormal pigments in the urine is an inconstant and unreliable sign of this generalised metabolic disorder

There are three chief types of porphyria (1) congenital (2) acute idiopathic and (3) acute toxic The first is a recessive congenital anomaly evident from infancy with pigmented urine pink teeth and bones and hydroa æstivale due to porphyrin photosensitization and without toxic symptoms The second variety is often familial and dominant appearing with abdominal and nervous symptoms in early adult life more commonly in females without pigmentation of the teeth and with skin sensitivity only rarely Acute toxic porphyria is clinically identical with the acute idiopathic form but is provoked by a recognisable toxic agent such as sulphonal veronal or a sulphonamide probably acting also in the presence of a latent constitutional

adult life the disease tends to chronicity and pleomorphism Visceral vascular involvement may give rise to pneumonitis with a typhus like skin rash or the myocardium kidneys liver, spleen or testicles may be involved In some cases the disease presents as an atypical encephalitis characterised by focal microglial lesions

The use of complement fixation tests (Warren and Sabin 1942) has indicated the probability of asymptomatic parental infections which may become manifest only in the child of an infected mother and it seems possible that the disease may account for some cases of mental defect and infantile choroidoretinitis of hitherto obscure ætiology The possible extent of this problem is indicated by the finding of serological evidence of such infection in ten per cent of unselected subjects between the ages of 20 and 35 tested in California (Frenkel 1949) and three per cent in Liverpool (MacDonald 1949) In some such surveys carried out in America the proportion of positive reactors particularly in the older age groups is such as to call into some question the specificity and significance of the tests used and further field surveys using stricter criteria of infection are necessary before the human distribution of the infective agent can be accurately assessed

Diagnosis Definitive laboratory diagnosis is in fact by no means easy The organism has occasionally been seen in centrifuged spinal fluid, which should also be injected intracerebrally into both mice and guinea pigs The simplest test is the toxoplasmin skin sensitivity reaction described by Frenkel (1948) but it is far from infallible It is usually positive in chronic cases but in acute cases it is often negative when clinical evidence and serological tests confirm infection and it is therefore employed more in field surveys than in diagnostic use In clinical diagnosis the complement fixation reaction (Warren and Sabin 1942) is widely used It was for some time considered that this test might also on occasion be negative in active congenital cases but if it is carried out as described by Sabin and Feldman (1949) in combination with an in vitro dye test for the demonstration of toxoplasma neutralising antibodies (Sabin and Feldman 1948) it appears to be highly reliable These workers accept negative results as excluding active *Toxoplasma* infection and stress the occasional occurrence of non toxoplasmic cases showing a very similar syndrome of choroidoretinitis and encephalopathy (Sabin and Feldman 1949)

The London School of Hygiene and the Department of Bacteriology at Sheffield University have experience of diagnostic methods in toxoplasmosis and have declared their willingness to assist in the investigation of suspected cases

Treatment Sulphonamides control the infection in experimental animals and acute cases have been successfully treated in children

who recover selective muscular wasting e g of the small hand muscles may remain and there may be recurrent attacks The cerebrospinal fluid is normal except that occasionally porphyrin can be detected

Pathologically scattered parenchymatous degeneration of peripheral nerves and of the ganglion cells of sympathetic ganglia spinal cord cerebellum and cerebral cortex with patchy demyelination is found In some cases there is a striking paucity of pathological findings Porphyrins are known to produce spasm of smooth muscle and Denny Brown and Sciarra (1945) suggest that the lesions of acute porphyria are primarily ischaemic and initially reversible

The neurological differential diagnosis includes acute infective polyneuritis catastrophic poliomyelitis familial periodic paralysis *progressive muscular atrophy and hysteria* There is no specific treatment although alkalis and calcium salts have been recommended When the anomaly is recognised toxic precipitating agents such as the barbiturates should be avoided

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NEUROLOGICAL MANIFESTATIONS OF HERPES ZOSTER

Although the virus of herpes zoster has not yet been identified and the relationship between zoster and varicella is still a subject of controversy clinical and pathological evidence makes it clear that the lesions of the disease are by no means limited to the posterior root and analogous sensory ganglia Pathologically involvement of the anterior horns even in the absence of paralytic signs was demonstrated by Lhermitte and Nicolas (1924) and Denny Brown *et al* (1944) demonstrated the existence of localised polio and meningo myelitis at the site of the lesions That widespread involvement of the neuraxis is present in most cases is suggested by the common finding of a raised protein content and lymphocytic response in the spinal fluid

Of the occasional clinical complications which appear to arise from wider dissemination of the virus a concomitant varicelliform eruption (zoster universalis) is not infrequent and may be due to a generalized spread of virus to the skin by way of the blood stream Clinical involvement of the lower motor neurone is most commonly seen in the form of *facial palsy* classically in geniculate herpes (Ramsay

metabolic abnormality Several observations indicate a close relationship between the various forms thus acute attacks may rarely occur in the congenital form, and families have been reported in which both idiopathic and toxic forms occurred Biochemical aspects are dealt with by Waldenstrom (1934) the origin of the abnormal pigments is obscure but evidence suggests a similar inborn defective enzyme system in all forms

Acute porphyria (Nesbitt 1944) represents then an idiopathic exacerbation of a chronic metabolic abnormality, several cases often occurring in families which also show much nervous and mental illness The patient frequently gives a history of recurrent attacks of abdominal pain with localised or complete paralytic ileus probably due to changes in the sympathetic ganglia and occasionally leading to laparotomy while jaundice, fever, leucocytosis and hypertension associated with renal damage may occur Pigmented oliguria may be a transient and occasional event not necessarily coincident with acute symptoms Spectroscopically the pigmented urine usually reveals the two absorption bands characteristic of the zinc complex of uroporphyrin and similar in location to those of oxyhaemoglobin while the addition of a few drops of hydrochloric acid yields the characteristic absorption bands of acid porphyrin Sometimes the urine may become dark only after standing this is due to the presence of colourless chromogen porphobilinogen which can be demonstrated by a simple test devised by Watson and Schwartz (1941) —

> Equal parts of urine and Ehrlich s reagent are mixed in a test tube and to the mixture is added an equal volume of a saturated aqueous solution of sodium acetate A few ccs of chloroform are then added and on mixing the red porphobilinogen aldehyde compound remains in the aqueous fraction that of urobilinogen being extracted in the chloroform

Nervous symptoms (Roth 1945) usually follow the abdominal cramps occurring at the height of the acute attack in about half of all cases They consist chiefly of flaccid pareses which may be distributed irregularly throughout the striated musculature and may be partial with retained electrical excitability Classically however these cases present as an acute severe polyneuritis with the clinical picture of an ascending Landry s paralysis proceeding to ptosis diplopia facial diplegia bulbar palsy and fatal respiratory failure in the majority Sensory loss is rare though pains and paraesthesiae occur particularly in the legs sphincter disturbances are frequent The deep reflexes are strikingly variable being often absent one day and present the next while irregular distributions such as retained ankle jerks with absent knee jerks may be found The syndrome may be accompanied by delirium more prolonged toxic psychoses fits focal cerebral signs and coma In the small proportion of patients

MOTION SICKNESS

The widespread use of small ships during the war and the increasing adoption of air travel have stimulated interest in this distressing minor malady and it has recently been the subject of considerable experimental study especially with regard to treatment In particular the war time papers of Holling *et al* (1944) and Noble *et al* (1947) provide valuable illustrations of the application of the experimental method to a practical problem of military urgency

Holling *et al* (1944) demonstrated the undoubted value of *hyoscine* in dosage of 1/100th grain in preventing seasickness on short journeys and also showed the relative ineffectiveness of non hypnotic doses of phenobarbitone and of amphetamine sulphate as well as of some proprietary remedies When however more prolonged protection is required as it may well be under military circumstances the toxic effects of hyoscine—excitement mental obfuscation hallucinations and dry mouth—are a distinct disadvantage and Noble *et al* (1947) found that *hyoscyamine* combined with hyoscine was better tolerated Even with the most effective hyoscine—hyoscyamine preparation however with or without added barbiturate little more than half the susceptible subjects are spared illness The degree of protection afforded by the administration of dummy tablets varies from nil to 50 per cent in the different experiments an observation not without interest in a condition with such an organic physiological basis

More recently McEvedy (1949) showed that *Anthisan* in doses of 100 mgms is about as effective as hyoscine The use of another new anti histamine drug *Dramamine* in motion sickness was similarly due to chance observation and Gay and Carliner (1949) produced a carefully controlled study showing results more favourable than any previously recorded According to these workers *Dramamine* in dosage of 100 mgm every five hours not only prevented symptoms in all but two of 134 men subjected to conditions which provoked sickness in 29 per cent of subjects treated with a dummy capsule but relieved established symptoms of seasickness within half an hour in 95 per cent of cases The capsules can be administered rectally if necessary and toxic effects have not been observed

The relief of established symptoms certainly presents a remarkable advance but that certain criticisms of Gay and Carliner s figures may be valid (particularly that conditions giving a higher incidence of sickness in the control groups are necessary in dealing with only moderate numbers) is suggested by the report of Strickland and Hahn (1949) whose results with the drug in experimental airsickness were less dramatic yielding a protection rate of only 71 3 per cent as against 44 4 per cent with a placebo

Hunt Syndrome) but also in trigeminal herpes with or without evidence of involvement of the geniculate ganglion Somewhat less common is *ophthalmoplegia*, usually involving the third nerve but sometimes the fourth or sixth as a complication of ophthalmic zoster possibly due to spread of the virus along connecting nerve fibres in the lateral wall of the cavernous sinus The cochlear and vestibular divisions of the *eighth nerve* also are sometimes involved separately or together alone or with other cranial nerve lesions Vertigo tinnitus and nystagmus may occur with or without deafness of very variable prognosis herpetic vesicles may be seen on the tympanic membrane or excoriation of the external meatus may be the only finding Variously distributed *segmental spinal cord paralyses* are usually limited to the region of the eruption, which precedes them by some days In their clinical course these lesions are somewhat similar to those of acute anterior polio myelitis showing slow but considerable improvement

Much rarer complications are partial *transverse lesions of the spinal cord* producing spastic monoplegia or paraplegia often with sensory loss These tend to appear between two and six weeks after the eruption and again show partial recovery Such cases should be carefully reviewed for evidence in the history or examination of pre existing nervous disease for some of them are undoubtedly cases of symptomatic zoster arising during the course of other spinal cord diseases

Rarer still are the cerebral complications which have a considerable mortality *Sudden hemiplegia* is not entirely limited to the elderly and the diffuse *encephalomyelitis* which can occur at any age has a high mortality Both in this latter group of cases and in occasional instances of apparently recurrent zoster serological tests (complement fixation) may help to distinguish the cases from herpes simplex

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MOTION SICKNESS

The widespread use of small ships during the war and the increasing adoption of air travel have stimulated interest in this distressing minor malady and it has recently been the subject of considerable experimental study especially with regard to treatment In particular the war time papers of Holling *et al* (1944) and Noble *et al* (1947) provide valuable illustrations of the application of the experimental method to a practical problem of military urgency

Holling *et al* (1944) demonstrated the undoubted value of *hyoscine* in dosage of 1/100th grain in preventing seasickness on short journeys and also showed the relative ineffectiveness of non hypnotic doses of phenobarbitone and of amphetamine sulphate as well as of some proprietary remedies When however more prolonged protection is required as it may well be under military circumstances the toxic effects of hyoscine—excitement mental obfuscation hallucinations and dry mouth—are a distinct disadvantage and Noble *et al* (1947) found that *hyoscyamine* combined with hyoscine was better tolerated Even with the most effective hyoscine—hyoscyamine preparation however with or without added barbiturate little more than half the susceptible subjects are spared illness The degree of protection afforded by the administration of dummy tablets varies from nil to 50 per cent in the different experiments an observation not without interest in a condition with such an organic physiological basis

More recently McEvedy (1949) showed that *Anthisan* in doses of 100 mgms is about as effective as hyoscine The use of another new anti histamine drug *Dramamine* in motion sickness was similarly due to chance observation and Gay and Carliner (1949) produced a carefully controlled study showing results more favourable than any previously recorded According to these workers *Dramamine* in dosage of 100 mgm every five hours not only prevented symptoms in all but two of 134 men subjected to conditions which provoked sickness in 29 per cent of subjects treated with a dummy capsule but relieved established symptoms of seasickness within half an hour in 95 per cent of cases The capsules can be administered rectally if necessary and toxic effects have not been observed

The relief of established symptoms certainly presents a remarkable advance but that certain criticisms of Gay and Carliner s figures may be valid (particularly that conditions giving a higher incidence of sickness in the control groups are necessary in dealing with only moderate numbers) is suggested by the report of Strickland and Hahn (1949) whose results with the drug in experimental airsickness were less dramatic yielding a protection rate of only 71 3 per cent as against 44 4 per cent with a placebo

Hunt Syndrome) but also in trigeminal herpes with or without evidence of involvement of the geniculate ganglion Somewhat less common is *ophthalmoplegia* usually involving the third nerve but sometimes the fourth or sixth as a complication of ophthalmic zoster possibly due to spread of the virus along connecting nerve fibres in the lateral wall of the cavernous sinus The cochlear and vestibular divisions of the *eighth nerve* also are sometimes involved separately or together alone or with other cranial nerve lesions Vertigo tinnitus and nystagmus may occur with or without deafness of very variable prognosis herpetic vesicles may be seen on the tympanic membrane or excoriation of the external meatus may be the only finding Variously distributed *segmental spinal cord paralyses are usually limited to the region of the* eruption which precedes them by some days In their clinical course these lesions are somewhat similar to those of acute anterior polio myelitis showing slow but considerable improvement

Much rarer complications are partial *transverse lesions of the spinal cord* producing spastic monoplegia or paraplegia often with sensory loss These tend to appear between two and six weeks after the eruption and again show partial recovery Such cases should be care fully reviewed for evidence in the history or examination of pre existing nervous disease for some of them are undoubtedly cases of symptomatic zoster arising during the course of other spinal cord diseases

Rarer still are the cerebral complications which have a considerable mortality *Sudden hemiplegia* is not entirely limited to the elderly and the diffuse *encephalomyelitis* which can occur at any age has a high mortality Both in this latter group of cases and in occasional instances of apparently recurrent zoster serological tests (complement fixation) may help to distinguish the cases from herpes simplex

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systems, and mentioned the occasional coincidence of venous thrombosis in the spinal cord Kendall (1948) agrees that this is theoretically possible but considers it anatomically improbable and points out that increase of platelets and fibrinogen and stickiness of the red corpuscles, are recognised puerperal changes which might provoke primary thrombosis at the site of damage to the endothelium of intra cranial sinuses Such damage could follow fluctuations of pressure during labour Phillips (1948) has shown that the blood in cases of puerperal thrombophlebitis shows a rise of fibrinogen B

In some cases of sagittal sinus thrombosis hydrocephalus is complicated by symptoms of focal cortical dysfunction caused by extension of thrombosis from the sinus to the cortical veins which drain into it The commonest of such symptoms which are usually sudden in onset are focal epilepsy monoplegia and hemiplegia More rarely apraxia or hemianopic visual symptoms may occur and in cases where the thrombophlebitis spreads to the veins over both hemispheres bilateral disturbances such as spastic weakness of both legs (cerebral paraplegia) may ensue In a proportion of cases arising under similar clinical circumstances focal signs attributable to cortical venous thrombosis may arise without evidence of hydrocephalus In some such instances there may be a superior longitudinal sinus thrombophlebitis insufficiently severe to impair absorption of cerebrospinal fluid while in others the process may have extended to cortical veins directly from an affected lateral sinus Occasionally however there may be no evidence of sinus involvement and the thrombophlebitis is apparently primary in the superficial veins Such an occurrence is found in a considerable proportion of puerperal cases

A third category of symptoms consists of cranial nerve palsies arising with or without hydrocephalus and focal cerebral signs The sixth nerve is most often involved and in the common otogenic cases this usually occurs on the side of the otitis and the lateral sinus thrombosis It is possible (Symonds 1944) that both this lesion and Gradenigo s syndrome (trigeminal pain and abducens palsy in association with otitis) may be due to direct involvement of the nerves by a similar inflammatory lesion of the inferior petrosal sinus Lesions of the ninth tenth and eleventh nerves are less frequent

Although otitic hydrocephalus may occasionally be preceded by a phase of meningeal irritation with cerebrospinal pleocytosis the fluid in the established condition is normal except for greatly increased pressure In puerperal cases also the fluid is usually normal the pressure being raised only if sinus involvement occurs either initially or by spread from thrombosed veins In fatal cases with complete obstruction of the sagittal sinus or where cortical thrombosis is extensive there may be microscopic or gross subarachnoid bleeding

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CEREBRAL THROMBOPHLEBITIS

While obstruction of the intracranial venous sinuses by infected thrombus is a familiar autopsy finding the symptomatology of milder non fatal cases of sinus thrombosis has recently been clarified by the papers of Symonds and Martin Such thromboses are often aseptic and may be associated with a similar thrombophlebitis of superficial cerebral veins

The occurrence of acute hydrocephalus following middle ear infections ("otitic hydrocephalus") has long been recognised The clinical picture, common in children and young people consists of the insidious onset of hydrocephalus with high papillœdema usually unaccompanied by serious constitutional disturbance and with less severe headache and vomiting than is usual in similar intracranial hypertension from other causes Such an occurrence is often accompanied by thrombosis of the lateral sinus on the side of the otitis, and Symonds (1937) has adduced clinical and pathological evidence that the usual sequence of events in such cases is extension of a mural thrombophlebitis from the lateral sinus into the superior longitudinal (sagittal) sinus where it leads to hydrocephalus probably by impairing absorption of cerebrospinal fluid through the arachnoidal villi or by obstruction of the venous outflow Many such patients make a rapid and complete recovery with or without repeated lumbar puncture and it is probable that the thrombus remains aseptic and organisation and recanalisation occur A similar clinical picture also based on superior longitudinal sinus thrombosis has been recorded after frontal sinusitis open and closed head injury with or without infection naso pharyngitis peritonsillar abscess peripheral venous thrombosis thrombophlebitis migrans and puerperal pelvic thrombosis

Cerebral thrombophlebitis occurring during the puerperium has recently attracted special attention Martin (1941) originally suggested that the intracranial thrombus in such cases might have formed round a nucleus reaching the sagittal sinus from the pelvic veins by way of the anastomosis between the pelvic and vertebral venous

systems and mentioned the occasional coincidence of venous thrombosis in the spinal cord Kendall (1948) agrees that this is theoretically possible but considers it anatomically improbable and points out that increase of platelets and fibrinogen and stickiness of the red corpuscles are recognised puerperal changes which might provoke primary thrombosis at the site of damage to the endothelium of intracranial sinuses Such damage could follow fluctuations of pressure during labour Phillips (1948) has shown that the blood in cases of puerperal thrombophlebitis shows a rise of fibrinogen B

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The chief diagnostic difficulties arise in cases secondary to local infections, particularly when hydrocephalic and focal signs are associated

In cerebral abscess there is usually a history of chronic rather than acute local infection, while the history of the condition itself is usually also much less acute and inflammatory signs in the cerebrospinal fluid are more prominent and more persistent It should be borne in mind however, that thrombophlebitis may initiate abscess formation and in doubtful cases exploration is advised

Prophylaxis resolves itself into the early chemotherapeutic and surgical treatment of infections In puerperal cases tight binders and straining should be avoided, and the patient should be propped up in bed when there is any reason to suspect pelvic thromboses Otitic hydrocephalus usually responds well to repeated lumbar punctures which aim to maintain the pressure at normal levels

Whether or not to use anticoagulant drugs is a matter of controversy In cases associated with local infections the tendency of the thrombosis to spread hardly seems marked enough to justify their employment In puerperal cases their cautious use has something to recommend it and it is remarkable that in such cases serious uterine bleeding seems to be a theoretical rather than a practical danger

Fortunately most patients with intracranial venous thrombosis *have an otherwise healthy vasculature, and the focal signs usually* show more marked and more rapid recovery than do those arising *from arterial thrombosis*

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CHAPTER X

ENDOCRINE DISORDERS

by

C L COPE

Eye changes in Graves Disease Antithyroid drugs Radioactive Iodine Hyperparathyroidism and Fibrous Dysplasia of bone Addison s Disease The pituitary adrenocortical system Adreno genital syndrome Hypo pituitarism Obesity

EYE CHANGES IN GRAVES' DISEASE

It is now well recognised that the classical ocular changes observed in hyperthyroidism are made up of a number of separate and largely independent phenomena of which the main are (1) retraction of the upper eyelid (2) true exophthalmos or forward protrusion of the orbit (3) varying degrees of external opthalmoplegia and (4) swelling of the eyelids These four factors occur together in varying degrees and are not always easy to separate without careful clinical observation Thus retraction of the upper lid gives a staring appearance to the eye and an erroneous impression of true exophthalmos whereas swelling of the lids may mask a tendency to lid retraction and may obscure a true exophthalmos These effects have frequently caused confusion Either upper lid retraction or true exopthalmos may occur separately in hyperthyroidism although usually the two are co existent Lid retraction is probably due to contraction of the levator palpebrae superioris muscle Stimulation of the cervical sympathetic nerve causes contraction of this muscle with resultant lid retraction Pochin (1939) has recently confirmed that this effect can be produced in man but he finds that although an appearance of exophthalmos results from such cervical sympathetic stimulation yet no true forward protru ion of the orbit can be detected by direct measurement while

this experimentally produced lid retraction differs from that encountered in hyperthyroidism In cervical sympathetic stimulation both lids tend to be retracted whereas in Graves disease there is little or no retraction of the lower lid Pochin concludes therefore that the lid retraction in Graves' disease is due to a spasm of the levator palpebræ superioris muscle produced in some manner other than stimulation of the cervical sympathetic

A great deal of research has recently been done on the mechanism of *exophthalmos* This has been stimulated in the main by the discovery that exophthalmos can be produced readily in suitable experimental animals by injection of thyrotropic hormone Careful comparisons have been made of this form of exopthalmos with that found in the human subject and the two are essentially similar in both anatomical and microscopic changes (Smelser 1937 Rundle and Pochin 1944) It is now generally agreed that in both forms the protrusion of the orbit can be dully accounted for by the increase in volume of the retro orbital contents Several factors contribute to this increase in volume The most important in man is an increase in amount of the retro orbital fat Some degree of ophthalmoplegia is a not uncommon finding in exophthalmic Graves disease and it seems probable that this is largely due to the mechanical interference with the function of the muscle by the fat deposited within at least in the milder forms

In experimental exophthalmos the protrusion can also be accounted for by an increase in volume of the retro orbital tissues but whereas in man this is largely due to fat in animals treated with thyrotropic hormone it is largely due to œdema fluid (Smelser 1937 Pochin 1944) The difference is probably due to the fact that the human exophthalmos is of very slow onset whilst the experimental is produced acutely in two or three days In the condition of malignant exophthalmos or exophthalmic ophthalmoplegia to be considered later œdema is undoubtedly a major factor in the development of the orbital changes

The development of exophthalmos in guinea pigs treated with thyrotropic hormone can be prevented by the administration of thyroid hormone It is pertinent to enquire therefore why in Graves disease the excess of circulating thyroid hormone does not exert a similar inhibition Though this has not been fully explained it is probable that the circulating thyroid hormone is insufficient in amount to produce appreciable effect It is significant that Pochin (1944) found no difference in the degree of exophthalmos in normal and thyroidectomized guinea pigs when both were treated with thyrotropic hormone In the human subject however there may well be a slight inhibitory effect for it has been shown by Rundle and Wilson (1945) that slight but fairly consistent increase of true exophthalmos

occurs after thyroidectomy for a toxic goitre though not for a simple one

Earlier ideas that sympathetic stimulation plays a part in the production of exopthalmos are now considered to be unjustified



Fig 31 Exophthalmic ophthalmoplegia with perforated right cornea B M R + 38 (*Case of Prof Ida Mann*)

Several investigators have stimulated the sympathetic in man without obtaining any measurable orbital protrusion

Exophthalmic Ophthalmoplegia (Malignant Exophthalmos)

Some mild degree of exophthalmoplegia is a common finding in Graves disease the most frequent form being a bilateral impairment of upward movement due to weakness of the superior rectus muscles But in 1938 Brain and Turnbull called attention to a much more severe clinical picture which they termed exophthalmic ophthalmoplegia Though it is probable that all gradations will be found between ordinary exophthalmos and this severe form yet exophthalmic ophthalmoplegia presents so many clinical points of difference and problems of treatment that it is convenient to regard it as a separate but allied clinical condition It is frequently associated with present or past disorders of thyroid function but this is not invariably so It may occur in hyperthyroidism with raised basal metabolic rate or

may develop some months or years after thyroidectomy at a time when the metabolic rate is either normal or below

In contrast to ordinary exophthalmos it is commoner after the age of 40 than before and is more frequent in men than in women It develops gradually over several months to a moderate or severe degree of exophthalmos which in one case was as much as two centi



FIG 32 Exophthalmic ophthalmoplegia with extreme œdema of conjunctival sacs B M R normal (*Case of Prof Ida Mann*)

metres There may be associated aching pain in the orbits Œdema of the conjunctivæ and lids follow and both may become extreme Indeed the œdema may reach such a degree that it causes complete eversion of the conjunctival sac over the eyelid in the form of a large pouch (Figs 31 and 32) Conjunctivitis soon results and corneal ulceration is very liable to occur Papillœdema is frequent and may lead ultimately to optic atrophy and blindness Eye movements are usually impaired and diplopia is common Upward movement is most frequently affected lateral next and downward movement least but in severe cases there may be a complete external ophthalmoplegia and corneal ulceration or even a panophthalmitis may necessitate enucleation of the orbit Because of these serious sequelæ the

condition has been called by some "malignant exophthalmos" It is probable that this condition is also a manifestation of disordered thyrotropic hormone—thyroid hormone balance though its nature is not yet fully understood The pathological changes resemble those produced in experimental animals by thyrotropic hormone

The treatment of these cases requires the aid of an ophthalmologist In the milder forms a temporary and partial relief from discomfort can be obtained by massaging away the œdema fluid from the eyelids The cornea should be protected by tarsorrhaphy so far as possible though if the lesion is still progressing this is very liable to break down In cases in which the basal metabolic rate is not raised considerable relief of symptoms may result from giving thyroid extract It should be tried cautiously (Mann 1945) When the basal metabolic rate is much raised thyroid hormone should not be given Iodine therapy causes little or no improvement Partial thyroidectomy should be avoided as it may further aggravate the condition Thiouracil also must be used with care as several cases of malignant exophthalmos have been made worse by it (Williams and Clute 1944)

Recovery has followed X ray irradiation of the pituitary gland and this is worth trial in resistant cases In some cases however even though severe spontaneous subsidence gradually occurs the condition of the eyes returning almost to normal In severe cases in which there is danger of sight being lost an operation for orbital decompression may be necessary In this operation devised by Naffziger (1933) the greater part of the roof of the orbit is removed and if papillœdema is present the optic foramen is also opened The operation results in considerable reduction of the exophthalmos and relief of symptoms Ida Mann however by careful medical and local treatment has been able to avoid the operation in a series of 18 consecutive cases

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may develop some months or years after thyroidectomy at a time when the metabolic rate is either normal or below

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a euthyroid state is reached as judged by resting or sleeping pulse basal metabolic rate and body weight The patient s own feelings may be an unreliable guide as a partial improvement may be interpreted by him as a complete return to normal When a normal state has been achieved maintenance doses must be continued for at least six months 100 to 200 mg of thiouracil or 50 to 100 mg of methyl or propyl thiouracil being average daily requirements

Results Some clinical improvement is usually apparent within ten days The basal metabolic rate falls roughly one per cent per day in primary hyperthyroidism A normal state should therefore be restored in four to six weeks Adenomatous toxic goitres often take about twice as long to react If iodine therapy has been used before thiouracil is started the response is much delayed but this delay may be reduced by continuing iodine through the first part of the thiouracil course Since thiouracil produces a hyperplastic reaction in the thyroid no early diminution in size or vascularity of the gland occurs and there may even be a mild increase in size In this the thiouracils differ from radio iodine Lid retraction is reduced but there is usually either no change or a slight temporary increase in exophthalmos The ocular changes are thus similar to those resulting from subtotal thyroidectomy Auricular fibrillation may cease under treatment in some cases in others quinidine may be desirable later

The restoration of biochemical and metabolic disturbances tends to parallel the clinical improvement The blood protein bound iodine falls from its previous high level to normal or even below Nitrogen and calcium loss is curtailed and creatinuria which is so frequent in hyperthyroidism is reduced A rise of serum cholesterol above normal may herald the onset of myxoedematous symptoms If this occurs the dose of thiouracil should be reduced or small amounts of thyroid given

A temporary cure may be expected in at least 75 per cent of cases and in a higher percentage of cases of primary hyperthyroidism If maintenance doses are continued for several months after the basal metabolic rate has fallen to normal the tendency to relapse is considerably reduced and this should therefore always be done The relapse rate varies considerably in different clinics It is much higher if treatment only lasts three months than if it is continued for 8 to 12 months It is less in mild than in severe cases and in women than men Of 119 patients treated by Williams (1949) for about a year 57 had complete remissions persisting for one and a half to four and a half years after cessation of therapy If a relapse does not occur within two years after treatment it is unlikely to occur later indeed it is usually apparent within six months There is no good relation between promptness of response to antithyroid drugs and liability to

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ANTITHYROID DRUGS

Although a wide variety of antithyroid substances are now known thiouracil and its derivatives are the only ones which are in general therapeutic use The thiouracils act by blocking the synthesis of organic iodine compounds including the thyroid hormone They do not prevent the storage of inorganic iodine by the thyroid gland but the production of thyroid hormone is suppressed and the stores of hormone already in the gland are gradually used up The resultant fall in circulating thyroid hormone stimulates the anterior pituitary to increased production of thyroid stimulating hormone This causes hyperplasia hypertrophy and increased vascularity of the gland Since no further thyroid hormone is produced the signs of hyperthyroidism disappear giving place if treatment is continued too vigorously to a state of myxœdema The paralysed gland can still store iodine but this remains in inorganic form Practically all cases of hyperthyroidism will respond to these antithyroid drugs if sufficient dosage is given The rate of response is variable and probably depends on the rate at which stores of preformed hormone are used up

In early trials with the thiouracils the occasional toxic effects encountered were stressed and great caution in their use was advised Longer experience has shown that these toxic effects which are described below are less serious than was first thought Methyl thiouracil and propyl thiouracil are less toxic than thiouracil itself and are to be preferred The thiouracils when given by mouth rapidly enter the blood stream Part is excreted by the kidneys part is destroyed and some concentrates in the thyroid gland Propyl and methyl thiouracil reach higher concentrations in both blood and thyroid tissue than does thiouracil Methyl thiouracil is about twice as active in man as thiouracil or propyl thiouracil All the thiouracils pass the placental barrier in active quantity and are concentrated in the breast milk

Dosage Initial dosage is now usually 500 to 600 mg of thiouracil or 300 mg of methyl or propyl thiouracil daily given three or four times a day by mouth Smaller doses initially may be desirable in mild cases or in pregnancy whilst toxic adenomatous goitres may need larger doses When the clinical condition is improving the dose should be moderately reduced and continued in the lower dosage until

is negligible but this high standard is not maintained everywhere The quality of the available surgery should therefore be a factor in making the choice for antithyroid drugs are preferable to mediocre surgery Good surgery however offers a more rapid and more permanent cure it removes an unsightly goitre but leaves a scar It involves often more time off work and there is a small risk of vocal cord paralysis or of hypoparathyroidism Antithyroid drugs are slower in action less certain to produce permanent cure and may have toxic effects They do not remove the goitre and can be given to outpatients who are continuing at work But good collaboration of patient with physician is essential for their safe use for those on antithyroid drugs must report promptly the onset of any symptom even a mild sore throat to the physician Since in the later months of treatment the patient may feel himself cured his close collaboration becomes less easy to retain Supplies of the drug should therefore be so limited that he has to return frequently for observation Those in whom for any reason good supervision cannot be maintained are unsuitable subjects for thiouracil Iodine alone is now seldom used except in preoperative therapy

Surgery is the treatment of choice in large nodular goitres in intrathoracic goitres in certain cases relapsing after adequate periods of thiouracil and when for psychological reasons it is desirable to avoid an atmosphere of chronic invalidism Sensitivity to thiouracil or *evidence of tracheal compression are other reasons for preferring* surgery

Antithyroid drug therapy is suitable for women over 30 with mild symptoms and a small goitre for those who refuse surgery and for those who are bad surgical risks especially from cardiac failure It is also useful for those who have relapsed after one or more partial thyroidectomies It will be used more frequently in areas where good thyroid surgery is not available but it is contraindicated when signs of tracheal compression are present

Resort to radio iodine may be made in those who have responded badly *to antithyroid drugs either from sensitivity or from relapse* and who are unwilling or unsuitable for thyroidectomy Excellent reviews on the choice of treatment have been written by Williams (1949) and by Himsworth Morgans and Trotter (1947)

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relapse but decrease of thyroid size and control by a small maintenance dose are good prognostic signs (Williams) The relapse rate is probably not appreciably different with methyl thiouracil provided that adequate treatment is given Meulengracht and Kjerulf Jensen (1948) studied carefully the effects of this drug Of 111 cases treated for a year and followed up for 9 to 35 months after this only ten relapses (nine per cent) occurred Relapses may often be controlled by a further course of antithyroid drugs

Toxic Effects Mild or serious toxic effects may be expected in about 13 per cent of cases on thiouracil (Van Winkle 1946) in about 11 per cent on methyl thiouracil, and in two to three per cent on propyl thiouracil The majority of the toxic effects are mild

Mild toxic effects include skin reactions enlarged lymph glands headache, diarrhœa and dyspepsia They need not call for cessation of therapy They are more frequent with large doses than with small Less common reactions are neuritis œdema of the legs and parotitis

Serious toxic effects include drug fever which may necessitate change of treatment and agranulocytosis

Agranulocytosis has proved fatal in several cases It occurred in 2 5 per cent of Van Winkle s (1946) series of 5 745 cases treated with thiouracil Its frequency is not related to the size of the dose Seventy per cent of cases occur in the first two months but no stage is immune A case has been reported after 12 months treatment Persons showing an initial mild granulopenia from other cause are not more likely to develop agranulocytosis than others when on thiouracils Onset is often sudden and routine blood counts are not of great help in predicting it Fever malaise and sore throat are better signs to watch for and the patient should be carefully investigated whenever any of these occur Prompt and vigorous treatment is needed including immediate cessation of the drug blood transfusion and large doses of penicillin A milder neutropenia is more common (4 4 per cent) It is an indication for greater care in treating the patient but does not necessarily contraindicate further thiouracil therapy

Exophthalmos A mild increase in exophthalmos is frequent during therapy with antithyroid drugs It is not usually of clinical significance but these drugs should be used with special care in cases of severe or of malignant exophthalmos Simultaneous thyroid administration in small doses helps to lessen this effect and does not materially interfere with the influence of the antithyroid drug on the hyperthyroid symptoms

Choice of Therapy Radio iodine though relatively cheap is not readily available and requires experience for its most effective use The initial choice lies therefore between surgery and the antithyroid drugs The mortality from thyroidectomy in the best thyroid clinics

is negligible but this high standard is not maintained everywhere The quality of the available surgery should therefore be a factor in making the choice for antithyroid drugs are preferable to mediocre surgery Good surgery however offers a more rapid and more permanent cure it removes an unsightly goitre but leaves a scar It involves often more time off work and there is a small risk of vocal cord paralysis or of hypoparathyroidism Antithyroid drugs are slower in action less certain to produce permanent cure and may have toxic effects They do not remove the goitre and can be given to outpatients who are continuing at work But good collaboration of patient with physician is essential for their safe use for those on antithyroid drugs must report promptly the onset of any symptom even a mild sore throat to the physician Since in the later months of treatment the patient may feel himself cured his close collaboration becomes less easy to retain Supplies of the drug should therefore be so limited that he has to return frequently for observation Those in whom for any reason good supervision cannot be maintained are unsuitable subjects for thiouracil Iodine alone is now seldom used except in preoperative therapy

Surgery is the treatment of choice in large nodular goitres in intrathoracic goitres in certain cases relapsing after adequate periods of thiouracil and when for psychological reasons it is desirable to avoid an atmosphere of chronic invalidism Sensitivity to thiouracil or evidence of tracheal compression are other reasons for preferring surgery

Antithyroid drug therapy is suitable for women over 30 with mild symptoms and a small goitre for those who refuse surgery and for those who are bad surgical risks especially from cardiac failure It is also useful for those who have relapsed after one or more partial thyroidectomies It will be used more frequently in areas where good thyroid surgery is not available but it is contraindicated when signs of tracheal compression are present

Resort to radio iodine may be made in those who have responded badly to antithyroid drugs either from sensitivity or from relapse and who are unwilling or unsuitable for thyroidectomy Excellent reviews on the choice of treatment have been written by Williams (1949) and by Himsworth Morgans and Trotter (1947)

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RADIOACTIVE IODINE

Radioactive iodine is in effect a form of 'labelled' iodine which behaves physiologically exactly like normal iodine yet can be detected and measured accurately in extremely small traces by means of suitable Geiger counters These counters record automatically the number of radioactive atoms disintegrating in a given time Radioactive iodine or I^{131} thus enables the course of iodine through the body to be investigated in considerable detail When a small and harmless dose (less than 100 microcuries) is taken by mouth in a small amount of water it rapidly enters the blood stream and starts to diffuse into the extracellular fluids Immediately both the thyroid gland and the kidneys begin independently to remove it from the blood stream Usually over 90 per cent is dealt with by these two organs less than ten per cent remaining in other tissues of the body The rates of uptake by the thyroid and of excretion by the kidney are both related to the concentration in the blood stream at any given moment Two main factors therefore determine the rate of removal of iodine by each organ in their mutual competition for the available dose Thyroid uptake at any moment is determined by (*a*) the activity of the thyroid and (*b*) the amount still in circulation which has not yet been removed by either thyroid or kidney The excretion rate by the kidney is determined mainly by (*a*) the degree of renal activity and (*b*) the amount of radio iodine as yet uncaptured by the thyroid or the kidney Since deviations from normal renal function are not usually of such degree in cases of suspected thyroid disease as to be a complicating factor these effects can readily be used to estimate the activity of the thyroid gland The mild impairment of renal function sometimes found in myxœdema is not a serious complication

It is found that in hyperthyroidism the rate of uptake of radio iodine by the thyroid is much greater than in the normal thyroid so that proportionately less is available for excretion by the kidney and a smaller proportion of the administered dose is excreted in 24 or 48

hours In myxoedema on the other hand iodine uptake by the thyroid is slow and small and a higher proportion than normal therefore appears in the urine The range of excretion values found in a representative series of patients is —

Normal	[illegible]—60 per cent in 48 hours
Hyperthyroid	10—[illegible]
Myxœdema	7[illegible]—[illegible]0

Tests using this principle may thus be of very great value in the diagnosis of suspected hyperthyroidism or myxœdema They can be carried out on hospital out patients They have a particular value in auricular fibrillation with cardiac failure and in other conditions where the basal metabolic rate is not a reliable criterion The only requirements of the test are the introduction of the tasteless and innocuous dose into a fasting stomach and the careful collection of all subsequent urine for two days Teams capable of analysing these specimens for radio iodine are increasing in number throughout the country and the test may be expected to establish itself as a routine diagnostic procedure in many centres

Certain precautions must be observed if fallacious results are to be avoided No iodine other than that occurring naturally in a normal diet should have been taken for two or more weeks before the test Thiouracil drugs thiocyanates and thyroid extract must be avoided for a similar time Renal function should not be seriously impaired and extensive œdema may also interfere with proper results Even in the absence of the above complicating factors anomalous results conflicting with clinical impression are occasionally met They may be particularly informative for they should suggest exogenous influences Thus a high iodine excretion in a subject with thyrotoxic signs should suggest that the latter are due to excessive thyroid administration Signs of myxœdema associated with a low iodine excretion should raise suspicion of a drug as cause of the myxœdema *Thiocyanate* which is sometimes given for hypertension can do this so also can *resorcinol* when absorbed through the skin of a chronic ulcer to which it has been applied (Bull and Fraser 1950)

The amount of radio iodine present in the thyroid gland at any time can be measured by a Geiger counter suitably placed close to the neck The rate of uptake of iodine into the gland after a test dose by mouth or intravenously can thus be measured directly Rapid uptake is characteristic of hyperthyroidism slow or minimal uptake is found in myxœdema and the method is of diagnostic value If the plasma content of radio iodine is simultaneously measured a thyroid iodine clearance can be measured analogous to the renal urea clearance Pochin (1950) believes that this will prove the most reliable test of thyroid activity The normal clearance rate varies from 7 to 42 ml per minute Even in mild Graves disease clearances of over 100 ml

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neoplasms however do not concentrate iodine and are thus immune to the toxic effects of the drug which does not reach a sufficient concentration in them It has been shown that some inert metastases will develop ability to take up the iodine adequately either after complete thyroidectomy or after injection of thyroid stimulating hormone In one series of 21 cases of non functioning metastatic thyroid cancers (Rawson, Marinelli *et al* 1948) eight developed ability to concentrate iodine after complete thyroidectomy The time required to produce the change varied from one to 32 months Thyroidectomy either surgical or by irradiation is thus a desirable preliminary to treatment of thyroid metastases with radio iodine In another representative series of 30 thyroid carcinomas (Seidlin Rossman Oshry and Siegel 1949) 12 were treated with radio iodine Seven are still living and improved, five have died Two have survived more than five years and biopsy has shown that metastases can lose all viable tumour tissue There is no correlation between dose administered and clinical result the concentration in the thyroid tissue itself is the variable but determining factor Sixty to 300 millecurie doses are usually given and are repeated at intervals Some depression of hæmopoietic tissue may occur as a side effect but great clinical improvement often accompanies the regression of the metastases

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HYPERPARATHYROIDISM

There has in the last decade been a very considerable clarification of the criteria necessary for a diagnosis of hyperparathyroidism and a greater appreciation of those conditions with which it is liable to be confused Much of this work has been due to Albright and his fellow workers (1934) who have been able to diagnose parathyroid adenoma in a number of cases in which the classical features of osteitis

per minute are usually found The test is thus a sensitive one and is independent of renal function changes It can readily be carried out on out patients and can be completed within an hour Trained workers are necessary if results are to be reliable

Direct measurement over the neck can be used to determine whether a thyroid adenoma or carcinoma has iodine concentrating power or not A toxic adenoma can be detected in this way The majority of thyroid neoplasms do not concentrate iodine and cannot be treated with radio iodine Demonstration of iodine concentrating power is thus an essential preliminary to treatment of thyroid neoplasms with this substance Metastases in lungs, abdomen or elsewhere may be similarly investigated for concentrating power prior to consideration of therapy

Radioactive Iodine in Therapy When radio iodine concentrates in thyroid tissue in sufficient concentration it emits during its dis integration gamma rays of sufficient intensity to be destructive to the thyroid cells The doses used for diagnostic investigation are well below the toxic level Larger doses have therapeutic value they cause hyperactive tissue to shrink and become inactive and neoplastic tissue to regress

In *hyperthyroidism* a single dose of 200 to 250 microcuries of radio iodine per gram of thyroid tissue will often control the condition The effective dose varies somewhat among individuals Myxœdema sometimes supervenes but can be readily treated by thyroid In one series of 46 patients (Soley Miller and Foreman 1949) the thyroid state was returned to normal within four months in 42 Transient tenderness of the thyroid and rise in basal metabolic rate may occur but both are usually mild and the gland diminishes progressively in size Recurrence may occur later and may be controlled either by ordinary iodine or by a further dose of radio iodine Williams (1949) has reviewed his experience of its use in a series of 109 cases It is a popular form of treatment with patients because of its extreme simplicity

Although no serious effects of radio iodine therapy have yet been reported there is a possibility that carcinoma or genetic effects may become manifest at a later date Because of this radio iodine therapy is at present being used with caution and is generally reserved for persons over 40 years of age and for those who for surgical or other reasons are poor surgical risks Cases showing recurrence after thyroidectomy have also been treated Thus radio iodine therapy should not generally be used for those cases suitable for surgery or responding well to antithyroid drugs

In *thyroid carcinoma* greater risks may be taken and the value of radio iodine therapy is more evident The majority of thyroid

Biochemical Criteria in Hyperparathyroidism The essential chemical changes in the absence of which hyperparathyroidism should very rarely be diagnosed are a raised serum calcium a low serum phosphorus and evidence of excessive excretion of calcium in the urine These changes must always be assessed with close reference to the clinical probabilities

Serum Calcium A rise in serum calcium concentration above the normal upper limit of 11 milligrams per 100 cubic centimetres occurs in the great majority of cases Considerable fluctuations in the serum calcium level above and below the average may occur so that a single normal figure should never be accepted as evidence that hypercalcæmia is absent Although in general the rise in serum calcium tends to be proportional to the severity of the disease yet many exceptions do occur well marked disease being sometimes associated with only a mild rise in serum calcium In the recent analysis of 24 cases by Keating and Cook (1945) serum calcium was always above 10 milligrams per 100 cubic centimetres in cases with well marked bone changes ranging from 10 4 to 18 milligrams with an avarage of about 15 milligrams But in cases with less evident or absent bone changes four had an average serum calcium within normal limits Of these one had typical osteitis fibrosa cystica the other three renal calculi It is very probable that these latter would have been missed in many clinics with less experience of the disease

A rise in serum calcium is not by itself adequate evidence of hyperparathyroidism even when suspicious radiological abnormalities are present in the bones Serum calcium tends to rise when serum protein concentration rises and this occurs frequently in multiple myelomatosis and sometimes in sarcoidosis and in generalised carcinomatosis of bone In multiple myelomatosis moreover a secondary parathyroid hyperplasia may develop and thereby increase still further the resemblance to primary hyperparathyroidism It is prudent therefore to interpret the serum calcium with reference to the plasma protein concentration

Serum Phosphate In spite of the rapid release of phosphate from bone and its rapid excretion in the urine the serum phosphate concentration is characteristically low in hyperparathyroidism The reduction may be slight however and figures range from 3 5 milligrams down to 1 5 milligrams per 100 cubic centimetres A markedly low serum phosphate may be a very useful diagnostic point especially if there are minimal bone changes In the relatively infrequent cases in which renal failure is present this tendency may be masked and the phosphate normal or even raised in the blood

Serum Phosphatase Alkaline phosphatase in serum is considered to provide an index of osteoblastic activity provided that liver damage is absent A rise above normal is usual in bone diseases in which new

fibrosa cystica were lacking A full review of the clinical features of the condition has been published by *Keating and Cook (1945) and an* extensive study of the relations of hyperparathyroidism to other bone diseases has been made by Snapper (1943)

It is now usual to distinguish between a primary and a secondary *form of hyperparathyroidism though the distinction is not a sharp* one *Primary hyperparathyroidism* is usually associated with an adenoma of the gland, removal of which brings cure But some cases of apparent primary hyperparathyroidism occur in which a *generalised hyperplasia of all four glands is present (Albright Sulkowitch* and Bloomberg 1938) This is particularly likely to be found among those cases lacking the developed picture of osteitis fibrosa cystica *Secondary hyperparathyroidism* is encountered as a complication *of chronic renal failure* (q v) in multiple *myelomatosis and* less commonly in generalised carcinomatosis of bone It is associated with a generalised hyperplasia of all four glands and when present may add considerably to the difficulty of diagnosis of the primary bone lesion

The classical form von Recklinghausen s osteitis fibrosa cystica which is associated with a parathyroid adenoma is well known but the presenting clinical picture is sometimes far less clear Thus in a series of 67 proved cases reviewed by Cope (quoted by *Keating and* Cook 1945) the classical picture of osteitis fibrosa cystica was present in only one third minimal or atypical bone lesions were found in another third, whilst the remainder lacked all evidence of bone involvement *It follows that many* cases *will be missed if the belief* persists that bony changes or symptoms are a necessary feature in the diagnosis of hyperparathyroidism

Hyperparathyroidism is associated with a large excretion of calcium and phosphorus *in the urine* and as a result *of this renal calculi* are very liable to develop and a history of recurrent calculus formation especially of calcium phosphate or oxalate stones should always raise the question of a possible causative hyperparathyroidism

Calcium salts may less commonly be deposited in considerable amount in the renal medulla In this event the case may present as one of impairment of renal function with nitrogen retention and the calcium deposition in the renal medulla may be revealed as a *fine stippling or more extensive shadows in the renal* X ray

In summary therefore the disease may present as (1) typical *osteitis fibrosa cystica* (2) *renal calculi* especially recurrent with or without osteoporosis (3) generalised *osteoporosis without cyst formation* and (4) *renal failure with calcified kidney* In all these types recourse must be had to biochemical investigations to establish the diagnosis

Under these conditions Keating and Cook (1945) found urinary calcium excretion rates ranging from 210 to 680 milligrams in 18 out of 19 cases studied. The majority were between 210 and 350 milligrams.

Treatment Specific treatment consists in discovery of and removal of the parathyroid adenoma. The tumour is rarely palpable. X ray of the œsophagus may give a hint to the localisation of the tumour by showing a deformity of the shadow. Adenomata may be multiple or the parathyroids may be embedded in the thyroid gland necessitating subtotal thyroidectomy. Any suspicious tumour found should be examined by frozen section before the operation is completed to exclude its being a thyroid adenoma or lymphoid tissue. Full surgical details have been discussed by Cope (1941). Occasionally a generalised hyperplasia of all four glands is present and in this event three of the four should be removed. Successful operation is indicated by a prompt fall in serum calcium to normal or below. There may occur under these circumstances tetany and oliguria. The onset of tetany is often determined more by the magnitude of the drop in serum calcium concentration than by the final figure. In cases with high pre operative phosphatase and heavy bone involvement tetany is particularly likely to occur owing to the rapid uptake of calcium by the recalcifying bones (Cope 1941). Continuous intravenous calcium gluconate may be necessary to overcome this hypocalcæmia in the early stages. Parathormone should not be used. Later intramuscular calcium is very valuable and oral calcium should be continued for several months after operation since the bones continue to absorb much calcium for a long period.

Fibrous Dysplasia of Bone

Albright Butler Hampton and Smith (1937) have called attention to an uncommon but important clinical condition which has frequently been confused with hyperparathyroidism. The syndrome described by them is characterised by *multi focal areas of osteitis fibrosa* associated with *patchy cutaneous pigmentation* and by *sexual precocity* especially in females. This condition has been reviewed by Falconer and Cope (1942) who described two typical cases. The syndrome is now accepted as a curious variant of a multifocal bone disorder separated as a clinical entity by Lichtenstein (1938) and called by him polyostotic fibrous dysplasia. In this a fibrous dysplasia of bone growing in the marrow spaces causes expansion and atrophy of the shaft.

Pathological fractures are common and gross bony deformity especially of the femur readily results (Figs 33 34). Affecting especially the long bones and the pelvic and shoulder girdles the radiological pseudocystic appearances may suggest osteitis fibrosa

bone formation is taking place even when bone destruction is simultaneously occurring Phosphatase is usually raised therefore in hyperparathyroidism when bone involvement is a prominent feature

A high serum phosphatase is frequently found in liver disease and in Paget s osteitis deformans but it may help in the differential diagnosis from multiple myelomatosis in which the serum phosphatase is usually normal

Unfortunately several phosphatase units are in common use and confusion may thereby be caused Normal figures are two to five Bodansky Units or 5 to 13 King Armstrong Units The latter unit is roughly one third of the former

Urinary Calcium Excretion The parathyroid hormone not only has a specific action in liberating calcium and phosphate from bones but also appears to have a direct action on the kidney leading to an increased urinary excretion of these ions

Barney and Sulkowitch (1937) have devised a simple clinical test which gives a rough and rapid indication of *hypercalcinuria* *Their* reagent is made up as follows —

> Oxalic Acid 2 5 grams Ammonium Oxalate 2 5 grams Glacial Acetic Acid 5 cubic centimetres and Distilled Water to 150 cubic centimetres

A small quantity of this reagent is mixed with an equal volume of urine which has been previously made acid to litmus with acetic acid The mixture is observed after two minutes In normal urines a faint turbidity is produced A marked or heavy milky precipitate rapidly indicates excessive calcium excretion If renal disease has been excluded a minimal precipitate by this test in a concentrated urine rules out hyperparathyroidism

Quantitative estimation of the urinary calcium output on a known and low calcium intake is of especial value in diagnosis Excessive excretion of calcium is an almost invariable finding The estimation is both simpler and of more value than a complete calcium balance experiment in which proper collection of the stools over a short period may be difficult Elmslie Fraser Dunhill and others (1933) have described three proved cases of hyperparathyroidism in two of which there was no negative calcium balance except on very low calcium intakes yet all three showed excessive urinary calcium excretion *In detecting such excessive excretion a fixed diet of known low calcium content* should be used Albright uses one containing 125 milligrams of calcium a day On such a diet most normal persons will excrete less than 100 milligrams of calcium in the urine per day Excretion rates between 150 and 200 milligrams are suspicious and figures over 200 milligrams a day definitely abnormal

Under these conditions Keating and Cook (1945) found urinary calcium excretion rates ranging from 210 to 680 milligrams in 18 out of 19 cases studied. The majority were between 210 and 350 milligrams.

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cystica This fibrous dysplasia differs from hyperparathyroidism however, in the following points (1) In spite of the multifocal pseudocystic appearance, X ray shows no tendency to generalised osteoporosis (2) Serum calcium and serum phosphorus are normal



Fig 33 Fibrous dysplasia of bone with sexual precocity (Albright syndrome) aged eleven (*Falconer and Cope 194_*)

(3) Serum phosphatase is *normal or only slightly raised* (4) There is no negative calcium balance or excessive urinary calcium *excretion* (5) The base of the skull often shows intense sclerosis in contrast to the frequent osteoporosis of hyperparathyroidism (6) It is a disease of youth becoming stationary in adult life

Fibrous dysplasia of bone is believed to be a developmental anomaly and is not associated with disorder of parathyroid function but fruitless search for parathyroid adenoma was often made before the nature of the malady was recognised



Fig 34 X ray of right femur of case shown in Fig 30 demonstrating pseudocystic appearance of bone

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ADDISON'S DISEASE

Diagnostic Tests In 1938, Cutler Power and Wilder introduced a diagnostic test designed for ambiguous cases This depended essentially on the fact that *the ability of the kidney to retain sodium* chloride under conditions of lack of this salt is markedly impaired *where there is adrenal cortical inadequacy The test distinguishes* fairly sharply between those with normal adrenal function and those with serious impairment It suffers however from the grave disadvantage that if applied to an advanced case of Addison s Disease the conditions of the test are very liable to precipitate a serious Addisonian crisis requiring prompt treatment (Willson, Robinson Power and Wilder 1942)

Because of this danger it seemed desirable to apply a less drastic preliminary test capable of detecting the more gross cases of adrenal insufficiency Robinson, Power and Kepler (1941) have accordingly introduced two simple clinical tests for this purpose The first of these is based on the empirically observed fact that patients with Addison s Disease fail to show the normal degree of diuresis following a rapid water intake The second test which is conveniently made at the same time as the first is dependent on the tendency of the *kidney in Addison s Disease to retain urea* whilst allowing the excretion of an excessive amount of sodium chloride The interpretation of both *tests is based on empirical findings in a large series of normal* and adrenal deficient patients

Test 1 Three ordinary meals are allowed on the day before the test but no extra salt is taken No food or drink is allowed after 6 p m The bladder is emptied at 10 30 p m and the urine then voided is discarded After this time all urine is carefully collected until 7 30 a m when the bladder is again emptied All urine voided during this night period is mixed and its volume is measured It is saved for subsequent use in Test 2 No breakfast is taken and the patient empties the bladder again at 8 30 a m and is then given a volume of water to drink equivalent to 20 cubic centimetres per kilo of body weight (9 cubic centimetres per pound) The total quantity of water should be drunk within 45 minutes The patient rests quietly in bed during the morning being allowed up only to void urine at hourly intervals between 8 30 a m and 12 30 when the test

is completed The volume of each of these hourly specimens is measured

If the volume of any hourly morning specimen is greater than the total volume of the night specimen then the test is considered negative and Addison s disease is unlikely If the volume of the largest hourly specimen is less than the volume of the night urine then the test is positive and Addison s disease is not excluded It is then necessary to proceed to the second test

Test 2 For this test the only additional requirements are a blood sample taken at the end of Test 1 and an analysis of the plasma from this and also of the mixed night urine specimen for urea and chloride From the figures so obtained a factor A is then calculated where A=

$$\frac{\text{Urine urea (mg\%)}}{\text{Plasma urea (mg\%)}} \times \frac{\text{Plasma Cl (mg\%)}}{\text{Urine Cl (mg\%)}} \times \frac{\text{Vol day urine}}{\text{Vol night urine}}$$

In this formula the volume of day urine means the volume of the largest hourly specimen in the morning specimens in Test 1 If the value of factor A derived in this manner is greater than 30 then there is probably no Addison s disease If A is less than 25 then Addison s disease is very probably present provided that sub acute or chronic nephritis diabetes insipidus and severe dehydration can be excluded

These tests have been tried out by their originators in 38 cases of Addison s disease and in 50 other persons Test 1 was never negative in Addison s disease A few persons not suffering from Addison s disease may give positive results in Test 1 but these can usually be excluded by Test 2 The administration of cortin or desoxycorticosterone acetate interferes with the tests and such substances should be omitted from treatment for at least two days before the test In occasional cases ambiguous results are obtained in both these tests In such circumstances the originators have found little extra advantage is gained by proceeding to the Cutler Wilder and Power test For this reason the details of this test are not given here and reference should be made to the original paper

Treatment Considerable experience has now been gained in the handling of cases of Addison s disease both with natural cortical extract and with the synthetic desoxycorticosterone acetate and a collected series of 158 cases has been published by Thorn Dorrance and Day (1942) It appears that the proportion of cases due to tubercle has fallen during the past 30 years being only 40 per cent in this series compared with 76 per cent in a series collected by Conybeare and Millis (1924) between the years 1904 and 1923 Cases

due to fibrosis are more likely to be responsive to replacement therapy for long periods than are those due to tubercle

Many of the milder cases of Addison's disease are greatly benefited and may be maintained satisfactorily for considerable periods by an increase in salt intake alone This salt may be added to the food taken in milk or given in enteric coated capsules with meals It is often well tolerated but may cause nausea or diarrhœa in some subjects The usual doses of extra salt aimed at should be from four to ten grams a day

A low potassium diet is now regarded as of doubtful value and has been known to produce a condition resembling family periodic paralysis In cases of milder type without urgent symptoms increased salt intake should always be tried before embarking on expensive replacement therapy but if with salt alone sufficient clinical improvement cannot be obtained or if more severe symptoms develop, then substitution therapy must be started Extra salt should then be reduced to about three grams a day, since injection of cortical extract or desoxycorticosterone acetate facilitates a rapid retention of sodium and of water in the body causing œdema, hypertension or dilatation of the heart with congestive failure If such signs are already present extra salt should be completely omitted

In cases of moderate severity desoxycorticosterone acetate is generally given in preference to cortical extract An average starting dose is five milligrams intramuscularly per day reduced later when the maintenance requirements are being determined The administration of this hormone will usually produce fairly rapid improvement in the lethargy the anorexia the muscular weakness the vomiting and the tendency to dehydration The blood pressure rises even to above the normal The disturbances in the electrolytes in body fluids are restored Total plasma volume is raised to normal or above and nitrogen retention if present is reduced Absorption of carbohydrates from the intestine is improved but carbohydrate metabolism is not fully restored to normal and a tendency to develop hypoglycæmia may persist

Signs of overdosage at this stage include (a) hypertension (b) generalised œdema (c) cardiac dilatation and congestive failure and may demand reduced dosage of both salt and hormone Hypoglycæmia is not an indication of overdosage but because desoxycorticosterone acetate unlike the natural extract does not fully correct the disorder of carbohydrate metabolism a tendency to hypoglycæmic attacks may remain but is usually controlled by frequent carbohydrate feeds

When satisfactory maintenance has been achieved by injection but not before the question of *tablet implantation* should be considered

While this has the advantages that it eliminates the need for frequent injections, provides a more steady supply and facilitates a more economical utilisation of the hormone it has the disadvantage that once tablets are implanted the dosage is no longer under control and that the rate of absorption varies appreciably so that dosage is not *accurately known* To provide some control over the therapy patients treated with tablet implantation should be in receipt of three to four grams *of extra salt daily so that this amount can be varied according* to their fluctuating needs Full details of the technique for handling patients treated by tablet implantation are given by Thorn Dorrance and Day (1942) Each 125 milligram tablet implanted is equivalent to an average daily absorption of about 0 5 milligram of hormone so that a patient who has been balanced on four milligrams a day will need in theory the implantation of eight tablets These tablets may be expected to provide a steady maintenance supply for six months or more after which time they will need renewal In actual practice daily requirements from tablets are rather lower than with injections and slightly less than the calculated number of tablets should be implanted

Addisonian Crisis A crisis in this disease is a serious medical *emergency calling for prompt and energetic treatment* which is directed to two fundamentally important factors the restoration of *plasma volume and of blood pressure on the one hand and neutralisa*tion of the tendency to hypoglycaemia on the other Thorn Dorrance and Day *(1942) recommend the following line of procedure* —

1 000 to 1 500 cubic centimetres of glucose saline with 25 cubic centimetres of aqueous adrenal cortical extract added is given intravenously An additional ten cubic centimetres of extract is given subcutaneously and this dose is repeated every two to four hours A further 1 000 to 1 500 cubic centimetres of glucose saline is repeated in 12 hours and then repeated daily until fluids are being taken well by mouth An initial dose of 20 milligrams of desoxycorticosterone acetate in oil is given intramuscularly in divided doses and five to ten milligrams are repeated daily Blood pressure is frequently determined If the systolic falls below 90 millimetres Hg an injection of one cubic centimetre of adrenalin in oil intramuscularly is indicated and the dose of injected desoxycorticosterone should be raised If however a fall of blood pressure occurs *in the presence of sodium* chloride and water retention then the number of infusions must be *reduced and further adrenal cortical extract given instead of desoxy*corticosterone acetate Plasma transfusions may be of help under *these conditions*

Cortisone in Addison s Disease It has long been recognised that *desoxycorticosterone does not provide* a complete replacement therapy

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many drugs and many infections cause a rapid loss of steroids cholesterol and ascorbic acid from the adrenal gland These changes are believed to be due to increased production of ACTH by the pituitary which in its turn is stimulated by the hypothalamus The changes in the adrenal are associated with an increased output of its glycogenic hormones probably cortisone and compound F There is an increased excretion of these in the urine One of the effects of these compounds is to lower the number of circulating eosinophil cells in the blood These conditions of stress are therefore associated with an eosinopenia *which tends to continue as long as overaction of the adrenal persists* This is a normal response to stress and its occurrence indicates a proper functioning of the pituitary adrenal system whilst its absence implies inadequacy of the system the commonest point of failure being *probably the adrenal gland itself The factor initiating this stimulation* of ACTH production has not been identified with certainty but the effect can be produced by adrenalin either intravenously or subcutaneously This action of adrenalin makes possible the testing of the system in a *simple clinical manner*

The Adrenalin Test A blood eosinophil count is done in the morning on the fasting patient and 0 3 mg of adrenalin is then injected subcutaneously Four hours later a second eosinophil count is done If the normal pituitary adrenal system is functioning a drop of 40 to 60 per cent in the eosinophil count will occur and this is independent of the absolute level of eosinophils except in allergic eosinophilia when the drop may be less A failure of the cells to fall or a drop of less than 30 per cent is indicative of inadequacy of the system The block may be in the adrenal the pituitary or possibly even in the hypothalamus *The test does not locate the site of the block but the* clinical background will frequently suggest the site of abnormality Thus in suspected adrenal inadequacy a negative response to the test is useful supporting evidence In hypopituitarism the test is also frequently negative but many cases of undoubted clinical hypopituitarism are encountered in which a positive response is obtained The test is thus of considerably less value in the diagnosis of hypopituitarism

Criticisms have been brought against the test on the theoretical grounds that spontaneous variations in blood eosinophil count may interfere In practice the test has proved a useful clinical tool when interpreted with discretion But if the result of the test is to be used to establish a diagnosis or as a justification for therapeutic action then it should be repeated two or three times to eliminate possible errors

If clinical evidence is lacking further help in localisation of the site of deficiency may be got by repeating the same test after an injection of 25 mg of ACTH instead of adrenalin

for Addison's disease, but that during periods of stress such as infection or operation, something more is needed For such emergencies adrenal cortical extract is generally used It now appears that cortisone provides much if not all of the hormonal action lacking in DCA

Cortisone can be given with advantage to many cases of Addison s disease who are not under special stress In doses of 15 to 30 mg daily there is improved appetite and gain in weight physical and mental capacity are improved and the tendency to hypoglycæmia is alleviated Cortisone is supplementary to and does not replace the use of salt with or without DCA which is needed to maintain electrolyte balance for the effect of cortisone on the electrolyte balance is minor and not to be compared with that of DCA Cortisone is especially indicated for those cases of Addison s disease which remain in sub normal health on optimal doses of salt and DCA It is also valuable for the relief of symptoms referable to a tendency to hypoglycæmia Fully documented reports on the long term effects of cortisone in this disease are not yet available It is likely that special caution will be needed in trying it on cases where the ætiology is tuberculous for there is experimental evidence in animals that cortisone lowers body resistance to tuberculosis If there is associated diabetes mellitus this may be aggravated by the cortisone for insulin resistance is increased Pellets of cortisone have been implanted with success, but these are not likely to be available for some time

In all periods of stress such as infection trauma operations and pregnancy larger daily doses are needed up to 200–300 mg per day

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THE PITUITARY—ADRENOCORTICAL SYSTEM

Much progress has been made in the last few years in elucidating the important role of the adrenal gland in conditions of stress of all types A wide variety of noxious stimuli including exposure to cold loss of blood physical trauma fractures surgical operations burns

anterior lobe *It is still uncertain whether these indicate primary* abnormality of the pituitary or whether they are secondary changes resulting from overaction of the adrenal cortex Since the changes described by Crooke may be present in adrenal adenoma when the opposite adrenal is atrophic it seems likely that the latter is the true explanation

The forms due to basophilism on the one hand and to adrenal tumour on the other are not with certainty distinguishable by clinical means The overlap between the two clinical pictures is very wide Although the name adrenogenital syndrome strictly implies a virilising state yet varying degrees of virilism of the female are frequently associated with several or even all of the classical features of the Cushing syndrome Thus hypertrophy of the clitoris is by no means invariable in adrenal tumours and its absence is of no diagnostic value

Aetiology of the Syndrome The fundamental abnormality appears to be an excessive production of adrenal hormones although the relative proportions of these may vary to produce differences in the clinical picture In some cases the excessive formation of cortisone like substances has been adequately demonstrated Cortisone itself given over long periods in sufficient dosage produces many of the changes seen in Cushing s syndrome The moon face the purple striæ the alkalosis and low serum potassium the increased insulin resistance all may be reproduced It is probable therefore that these and other features of the syndrome are due to excessive production of cortisone like products Hypertrichosis and virilism are when present manifestations of increased androgen production

The diversity of gross pathology which may result in the basic overaction of the pituitary adrenocortical system is well revealed in the analysis by Gorsuch (quoted by Kepler 1949) of 72 fatal cases all showing a well developed Cushing syndrome These showed —

Pituitary basophil tumour only	11
Combined pituitary and adrenal lesions	24
Pituitary (nonbasophil) tumour	6
Adrenal cortical adenoma	8
Adrenal cortical carcinoma	7
Adrenal cortical hyperplasia	9
Neither pituitary nor adrenal change	7

It seems therefore that a lesion causing overaction at either end of the pituitary adrenal axis can *produce the syndrome and that the site of* abnormality is not to be deduced from the character of the clinical changes Yet differential diagnosis of the two main causes of the syndrome is of prime importance because treatment is radically different—surgical removal of the adrenal tumour or irradiation of the pituitary gland

The ACTH test The patient is fasted overnight In the morning 25 mg of ACTH in saline is given intramuscularly Blood eosinophils are counted before and four hours after the injection In normals a drop of 50 to 90 per cent occurs in secondary hypoadrenalism due to pituitary deficiency a smaller fall of 45 per cent or less occurs whereas in Addison s disease no significant drop will usually occur The test may thus help to distinguish between primary and secondary adrenal deficiency

The *eosinophil counts* for these tests can be made directly without a full differential count if suitable diluents are used An eosin acetone water diluent stain is often used and is advocated by Thorn but this causes fairly rapid lysis of the eosinophils and also evaporates quickly so that agility and practice are required for its effective use In *agreement with Henneman et al (1949) we have found the method of Randolph (1944) to be preferable* The diluting stain in this is a freshly made mixture of equal parts of 0 1 per cent phloxine and of 0 1 per cent methylene blue each dissolved separately in 50 per cent aqueous propylene glycol Impure methylene blue is unsatisfactory The eosinophils are very stable in this mixture and are readily counted but they take about ten minutes to stain well and settle more slowly in the counting chamber

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ADRENOGENITAL SYNDROME

The clinical condition now well known as Cushing s syndrome was originally presented by Cushing (1932) as due to a basophil adenoma of the anterior lobe of the pituitary gland but cases were soon reported in which the sole cause was proved to be a tumour of the adrenal cortex or rarely even of the thymus If no adrenal tumour is present there is often hyperplasia of the adrenal cortex and it is probable that even when adrenal pathology is absent overfunction of the gland forms the basis of some of the symptomatology In 1935 Crooke showed that cases of the syndrome due to any cause have also in common a characteristic hyaline change in the basophil cells of the pituitary

anterior lobe It is still uncertain whether these indicate primary abnormality of the pituitary or whether they are secondary changes resulting from overaction of the adrenal cortex Since the changes described by Crooke may be present in adrenal adenoma when the opposite adrenal is atrophic it seems likely that the latter is the true explanation

The forms due to basophilism on the one hand and to adrenal tumour on the other are not with certainty distinguishable by clinical means The overlap between the two clinical pictures is very wide Although the name adrenogenital syndrome strictly implies a virilising state yet varying degrees of virilism of the female are frequently associated with several or even all of the classical features of the Cushing syndrome Thus hypertrophy of the clitoris is by no means invariable in adrenal tumours and its absence is of no diagnostic value

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Diagnosis Since the adrenal tumour is the more easily treated it is wise to regard every well developed case of the syndrome as a suspect tumour and to diagnose basophil adenoma of the pituitary only after its exclusion Every effort should therefore be made to obtain evidence of a tumour Sometimes a mass may be palpable in one loin or the pyelogram may show a downwardly displaced kidney A much more valuable technique is that introduced by Cahill (1935) in which an X ray is taken after introduction of air into the perirenal tissues through a needle so that the adrenal gland is outlined Air embolism has been reported as a complication but the risk should be small if care is taken Nevertheless some clinics prefer direct surgical exploration

The 17 ketosteroid excretion in the urine can be of considerable help in diagnosis and a high figure may even provide the first clue to an adrenal disorder The normal range of excretion varies somewhat in different laboratories but in general normal adult males show excretions of 6 to 20 milligrams and normal females during the reproductive years of 5 to 15 milligrams a day In a comprehensive review of the known facts about the 17 ketosteroids by Mason and Engstrom (1950) data are collected from the literature about the various types of adrenal disorder These support the general statement that excretions in excess of 50 mgms a day are suggestive of adrenal tumour The higher the ketosteroid excretion the more probable adrenal tumour becomes, and a figure of over 150 mgms in a woman is practically diagnostic But some adrenal tumours may show an only slightly raised output and we have seen a ketosteroid output of 70 to 80 mgms in Cushing s syndrome due to proved diffuse adrenal hyperplasia When the 17 ketosteroid excretion lies in the region of overlap common to both cortical tumour and to hyperplasia help may be obtained by determining the beta fraction after precipitation with digitonin This fraction consists largely of dehydroisoandrosterone and is increased in adrenal cortical tumour If with a total output of over 50 mgms a day more than 50 per cent is beta fraction then tumour is very much more probable than hyperplasia In pituitary basophilism the excretion of 17 ketosteroids is usually only a little above the normal range

The behaviour of another group of steroids the urinary reducing steroids, does not parallel that of the ketosteroids This group is as readily estimated in the laboratory as are the ketosteroids Several methods are at present in use for analysing them and normal figures vary considerably with the method In pituitary basophilism the excretion of reducing steroids is greatly increased from three to ten times the normal whereas in adrenal hyperplasia and tumour there is often only a slight rise above the normal This fraction reflects better

the cortisone metabolism than does the ketosteroid indeed cortisone itself is a reducing steroid *It represents only a small fraction of the total excreted however and the urinary excretion of cortisone like substances does not closely parallel the output of reducing steroids*

Treatment In considering treatment the above considerations will guide action An adrenal cortical tumour should be presumed to be present until it is proved to be absent since it is the more readily treated If no downward displacement of either kidney can be radiologically demonstrated and air insufflation reveals no definite adrenal tumour then exploration is still called for Much can be learned from seeing one adrenal It may contain the tumour sought it may be hyperplastic (in which case both adrenals are probably hyper plastic) or it may be atrophic in which case a hyperfunctioning tumour is likely to be present on the other side

In removing an adrenal cortical tumour the probability should be borne in mind that the opposite gland has undergone compensatory atrophy *The sudden loss of functioning tumour at a time of operational* stress may precipitate an Addisonian crisis calling for prompt treatment *Walters and Kepler* (1938) *advocate* pre operative salt and adrenal cortical extract for this reason and a close watch postoperatively for symptoms of acute adrenal failure Kepler (1949) has treated four cases of adrenal hyperplasia with fully developed Cushing s syndrome by subtotal adrenalectomy Two of these ultimately died but two steadily improved The procedure is hazardous and not yet established as an orthodox one

Pituitary basophilism sometimes responds well to X ray irradiation of the pituitary gland but failures with this therapy are frequent Œstrogens have been shown experimentally to depress pituitary function and they are worthy of trial if results of irradiation are *inadequate Dunn (1938) treated 11 cases with large doses and found* improvement in all but these results have not been generally con firmed Testosterone may improve the general condition and help to minimise the muscle wasting but cannot be regarded as curative

Hirsutism There is a large and important group of women who develop hirsuties with or without evidence of other endocrine dis turbance such as amenorrhœa oligomenorrhœa or enlarged clitoris but without showing the other features of the adrenogenital syndrome Many of these show a moderate rise in 17 ketosteroid excretion and this rise may be indicative of adrenal hyperplasia (Broster 1940 Hamblen Cuyler and Baptist 1941) Bissell and Williams (1945) *who studied a group of hirsute women found many cases with no rise* in 17 ketosteroid excretion and we have seen such cases Though many hirsute women probably have no adrenal hyperplasia others may have and the distinction is difficult Evidence of other endocrine

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ill may also develop such necroses though less commonly The extent of the necrosis is in general roughly proportional to the patient s condition at delivery and the extent also determines the severity of *the symptoms which the patient will slowly develop at a later date* It is probable that at least 80 per cent of the anterior lobe must be destroyed before severe symptoms are produced

Whilst is is believed that the pituitary necrosis occurs at the time of the stormy delivery symptoms may be mild or apparently absent *until* months or even years later *During the puerperium* such symptoms as may occur are liable to be attributed to the weakening effect of the illness at the time of delivery but a usual feature at this time is the failure of normal mammary activity the breasts shrinking and remaining dry

Later the restoration of rhythmic ovarian function fails Menstruation does not return and there may occasionally be menopausal flushings In severe cases there may be not only an amenorrhœa but a complete genital atrophy including superinvolution of the uterus shrinkage of the vagina and vulva and atrophy of the ovaries In mild cases a scanty and irregular menstruation may be resumed from 9 to 18 months after delivery and in such cases genital atrophy does not occur But even persistent amenorrhœa does not necessarily exclude the development of a subsequent pregnancy

There follows a slowly progressive loss of axillary and pubic hair varying from a thinning in the mild cases to a complete loss in the more severe It may take several years to become complete but did eventually become complete in 27 of the 51 cases collected by Sheehan During these and later years there may develop insidious personality changes There is asthenia and disinclination to work There is often dullness and mental apathy leading to forgetfulness and neglect of home and family duties Changes in general appearance ensue corresponding broadly in degree to the severity of the condition In the mildest there may be none but in the majority there is a hypothyroid appearance progressing often to a frankly myxœdematous *facies* with coarse features *thin head hair scanty eyebrows* and dry skin In the most severe and rapidly progressive the appearance may be one of premature senility with drowsy look and wrinkled dry yellowish and inelastic skin In Sheehan s series eight cases were of this type 27 were of frankly myxœdematous appearance *and ten showed a less markedly hypothyroid appearance* There may be no loss of weight but if loss occurs it is usually slight Severe loss of weight is an unusual feature

In conformity with the clinical appearance the basal metabolic rate is typically low It was generally between −25 and −33 per cent in Sheehan s cases but may be even lower *Signs suggestive of adrenal*

abnormality is in favour of hyperplasia but the degree of hirsutism is not of value in differential diagnosis Even extreme hirsutism is not necessarily incompatible with the successful completion of pregnancy

The treatment of hirsutism whether hyperplasia is suspected or not remains unsatisfactory Unilateral adrenalectomy has been practised by Broster (1938) and good results claimed, but the experience of other workers has often been less favourable Treatment with hormones has little success Large doses of œstrogens do not usually influence the condition, and local application of an œstrogen containing ointment is no more successful

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HYPOPITUITARISM

Post-partum pituitary necrosis The great majority of cases of hypopituitarism in women are now believed to be due to post partum necrosis of the pituitary anterior lobe Sheehan (1939) in an important paper on the subject has fully established post partum hypopituitarism as a clinical entity and has fully described the rather variable clinical picture Sheehan maintains that nearly every woman who suffers serious hæmorrhage or collapse at childbirth develops a large pituitary necrosis and that women who have been only moderately

Anorexia Nervosa is a special cause of confusion but the differences from hypopituitarism are well defined. Severe weight loss is uncommon in hypopituitarism and much of the confusion arises from the erroneous belief that this is not so. In anorexia nervosa the axillary hair and pubic hair are not lost; there may even be an increased growth of fine hair on cheeks, trunk and limbs. Unlike hypopituitarism the mental state is unusually active and there is great emotional instability suggesting a hysterical or even psychotic background unless the patient is in the final stages of the disease when apathy may finally supervene. The loss of appetite in hypopituitarism is mild and passive, being related to the apathy. In anorexia nervosa it is very active and indeed a major feature of the malady. Patients may show great ingenuity in avoiding the ingestion of food and in deceit. Anorexia nervosa is most common in young unmarried girls below the age of 30, whereas most women with hypopituitarism give a stormy obstetric history. Anorexia nervosa can frequently be traced to a strong emotional upset such as a broken engagement or a severed attachment to a close friend or relative of the same sex, whereas the hypopituitary patient is usually indifferent to such emotional stresses. To firm and sympathetic handling together with insistence on a proper intake of food the case of anorexia nervosa will usually respond, although a small percentage resist all such treatment and die. Such treatment will never benefit the true hypopituitary patient. When severe wasting is encountered in the absence of evident organic disease hypopituitarism should not be diagnosed until anorexia nervosa has been carefully considered and definitely excluded. Wasting of the degree encountered in anorexia nervosa is unlikely to be produced by organic disease without some physical signs of the cause being evident on careful examination.

Objective Tests of Hypopituitarism. Fraser, Albright and Smith (1941) have described two tests which are of considerable value in differentiating hypopituitarism from other conditions with which it may be confused.

The first of these is an *insulin tolerance test*. This involves the following of the blood sugar level for two hours after the injection of a standardised dose of insulin intravenously. In normal subjects the physiological mechanisms restore the blood sugar to the fasting level or above in two hours. These mechanisms are believed to be dependent on the proper functioning of the diabetogenic hormone of the pituitary gland and on the active functioning of the adrenal cortex and medulla. In hypopituitarism these mechanisms are impaired and as a result the blood sugar depressed by insulin fails to return to its pre-injection level within two hours. In ten cases of hypopituitarism studied by Fraser and Smith (1941) the blood sugar had a mean value of only

failure are much less definite than those referable to thyroid atrophy The Kepler test is often positive but the blood eosinophil drop in response to adrenalin may be normal in the same patient Blood pressure is occasionally low but is usually within normal range Pigmentation does not develop even in response to strong sunlight and nitrogen retention does not occur Fasting blood sugars tend to be lower than normal and there may be a liability to hypoglycæmia There is frequently a normochromic or slightly hypochromic anæmia of moderate degree The condition is very slowly progressive and death may occur in a few years, but is more commonly delayed for 20 years or more Some patients die of intercurrent infection but a common cause seems to be a short coma sometimes but not always associated with a severe hypoglycæmia

At autopsy the pituitary gland is small and contains usually less than ten per cent of the normal amount of anterior lobe tissue The posterior lobe is usually normal The thyroid gland is small and atrophic, and the adrenals are small and show cortical atrophy often of severe degree The thoracic and abdominal viscera are often abnormally small

Diagnosis of Hypopituitarism Sheehan and Summers (1949) have made an extensive review of hypopituitarism from all causes This confirms the frequency of obstetric accidents in the ætiology The clinical features in the latter group does not differ materially from that in cases due to other causes These authors discuss at length the difficulties of diagnosis

The commonest error is to diagnose one gland as deficient without recognising the more general syndrome Myxœdema responding poorly to thyroid is often diagnosed Superinvolution of the uterus may be diagnosed if the patient comes to a gynæcologist or a diagnosis of prolonged post partum debility may be attached The case may come to the hæmatologist as one of refractory anæmia Hypoglycæmia may be discovered and dismissed as idiopathic Mental torpor may lead to a purely psychological diagnosis or the woman may neglect her children and be classed as a problem mother or as merely lazy

Perhaps less often the endocrine basis is missed altogether The puffy face may suggest nephritis if albuminuria happens also to be present The mental slowness and maskhke expression may suggest Parkinsonism We have ourselves diagnosed diarrhœa associated with hypochlorhydria in one male case which was later proved The terminal coma is often of unusual type and difficult to diagnose Even in the known case of hypopituitarism the cause of the coma is not always clear Sheehan and Summers recommend that in all cases of obscure coma the pubic hair should be inspected

is not always zero in proved cases of hypopituitarism Typical abnormalities in both tests are strongly suggestive of hypopituitarism provided that Addison s disease and severe liver disease have been excluded but myxoedema may cause confusion Fraser and Smith believe that myxoedema can be differentiated from hypopituitarism in which the basal metabolism may be equally low by the observation that in myxoedema the blood sugar takes longer than 30 minutes to fall to its minimum and that primary myxoedema responds well to thyroid therapy whereas hypothyroidism secondary to hypopituitarism is not so relieved and may even be aggravated Additional aid in doubtful cases may be obtained from the response to injected thyrotropic hormone Anorexia nervosa may give a normal or abnormal insulin tolerance test but 17 ketosteroid excretion is never found reduced completely to zero though it may be low In hypopituitarism of sufficient degree to cause wasting 17 ketosteroid excretion is likely always to be zero so that the distinction can be made by this test though it should rarely be necessary

The eosinophil cell response to adrenalin injection described in the Pituitary Adrenocortical System section (page 327) may be of additional value but this test seems to be more informative in Addison s disease than in hypopituitarism in which a positive response is not infrequently encountered

Treatment With modern hormone therapy much can be done to improve the condition of patients with hypopituitarism Four main aspects of their secondary hormonal deficiency can be alleviated by replacement therapy—thyroid deficiency testosterone lack desoxycorticosterone lack and probably also cortisone lack These four are not equally deficient in all cases and efforts should be made to assess the extent of each Thyroid deficiency is assessed by appearance plasma cholesterol and basal metabolic rate Need for testosterone is indicated by lassitude muscle weakness and loss of weight Extra salt with small doses of desoxycorticosterone should be given to most cases but especially if the Robinson Power Kepler test is positive Testosterone itself has mild sodium retaining powers Cortisone will probably prove of great value if there are any signs of a tendency to develop hypoglycaemia but its use for this purpose has not yet been adequately explored

Patients with hypopituitarism are sometimes very sensitive to thyroid and increased loss of sodium may precipitate an Addisonian crisis It is wise therefore to give extra salt and 2 to 5 mg of desoxycorticosterone daily for a week or two before thyroid is started and it should then be given in small doses (0 5 to 1 0 grain daily) at first increasing this later if necessary Desoxycorticosterone therapy is best continued by implant of pellets subcutaneously A 100 mg pellet

63 per cent of the original fasting level two hours after the injection This phenomenon is the basis of the proposed test for hypofunction of the pituitary gland For its proper application other conditions which may give a similar response must be excluded by other means The main interfering factors are an abnormally high or low initial blood sugar (i e outside the range of 60 to 100 milligrams) hyperinsulinism Addison s disease severe liver disease and malnutrition Since the previous carbohydrate content of the diet affects the insulin response, this should be standardised at between 250 and 400 grams daily for at least four days before the test The insulin dosage used is 0 1 unit per kilo body weight but this may require modification in persons who are much under or over weight A blood sugar fall to below 45 per cent of the fasting level is aimed at and this should be reached within 30 minutes Serious hypoglycæmic symptoms such as clouding of consciousness or much fall in blood pressure should be carefully watched for and may call for an immediate termination of the test by giving adrenalin and sugar If severe hypopituitarism is suspected less insulin (0 033 units per kilogram) should be given for the test since the smaller dose may be expected to cause the requisite fall in blood sugar A blood sugar at two hours after the insulin injection which is still below 80 per cent of the fasting level may be regarded as abnormal in the test For further details of technique and precautions the original paper of Fraser and Smith (1941) should be referred to

The second test is an assay of the *17 ketosteroid excretion* in the urine The source of these ketosteroids is believed to be mainly the adrenal cortex with a smaller proportion derived from the testes in the male Excretion is therefore much reduced in conditions associated with cortical atrophy such as Addison s disease and hypopituitarism In Addison s disease a small excretion may persist derived from the still active testes in the male but in hypopituitarism testicular atrophy is a usual accompaniment and 17 ketosteroid excretion therefore falls practically to zero Normal excretion varies in women from 5 to 15 milligrams per 24 hours and in man from 6 to 20 milligrams Significantly reduced excretion is found in male hypogonadism in Addison s disease in severe malnutrition, before puberty, and in the aged Excretion falls to zero in most cases of hypopituitarism in Addison s disease in the female and in myxœdema it may also be very low in steatorrhœa and in cirrhosis of the liver These conditions which may interfere with the interpretation of the result must be excluded as far as possible by the usual clinical methods

Interpretation of the two tests in relation to hypopituitarism is best done by considering them together It must be made with due regard to the clinical probabilities A normal result in either test is in general good evidence against hypopituitarism though 17 ketosteroid excretion

specific dynamic action of proteins and other foodstuffs is not abnormal in the obese Demonstrable endocrine upsets are a relatively infrequent accompaniment of the more severe forms of obesity Myxœdema is not so often accompanied by obesity as is often believed Plummer (1940) found increased weight in only 60 per cent of a series of 200 cases of myxœdema and in most of these it was mainly due to water retention Clearly diagnosable forms of hypopituitarism though not necessarily associated with loss of weight rarely show appreciable gain In Cushing s basophilic syndrome the obesity is mild being less than at first sight appears owing to the false impression produced by the prominent chest cage and the shortening of the spine resulting from the associated osteoporosis No evidence of hypopituitarism can be obtained in the great majority of cases of obesity It is probable that the hypothalamus can play a part in the production of obesity Damage to the hypothalamus from chronic encephalitis is sometimes accompanied by considerable gain in weight though loss is more usual (Greene 1939) Encephalitis however is a rare cause of obesity

Newburgh (1942) has reviewed thoroughly the whole subject and his paper is worthy of careful study He concludes that the fundamental cause of obesity in man is overeating and believes that this is often due to psychological maladjustment Williams and his associates (1948) analysed possible ætiological factors in a series of 96 obese women and 50 normal controls The following findings are of interest —

	Obese group per cent	*Normal group per cent*
Obese parents	60	20
Obese siblings	25	3
Family hypertension	40	3
History of head injury	10	1
Unhappy childhood	22	nil
Food for nervousness	41	22
Irregular menses	15	1

Heredity thus appears as a more important factor than social maladjustment but the latter should not be ignored

Treatment The difficulty in using dietary restriction for the treatment of obesity has always been the conflict between the patient s ingrained dietary habits and his desire to lose weight Provided that the former can be sufficiently controlled by the latter weight will be progressively lost The caloric intake at which loss of weight commences varies considerably in different individuals and must usually be a matter of trial Failure to lose weight on a given diet can be due to three causes Either (1) the diet is not being adhered to or (2) the calorie content of the prescribed diet is too high or (3) water retention is occurring temporarily Cases are occasionally encountered in whom there is disappointing failure to lose weight on a diet of 800 calories or

will supply about 1 milligram daily Testosterone preferably also given as implanted pellets (three of 100 mg each) will speedily improve the feeling of well being diminish the earthy pallor of the face and increase the general strength It also encourages nitrogen retention and is indeed, a most valuable drug in the therapy of this disease If pellets are renewed at intervals the improvement may be maintained for long periods In times of stress such as during infections, cortisone is likely to be a valuable additional treatment

Sheehan and Murdoch (1938) were impressed with the benefit resulting from a subsequent pregnancy and recommended that patients be encouraged to embark on one Clearly every precaution must be taken to ensure that no obstetric complication occurs at this delivery Probably the new pregnancy stimulates the hypertrophy of the remaining intact pituitary tissue We have seen two cases who had a later pregnancy Both reported a marked improvement persisting after delivery but in neither was the improvement maintained for more than a few months

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OBESITY

It is becoming increasingly realised that the primary factor in the great majority of cases of obesity is excessive eating and that any demonstrable disorder of metabolism is a rare accompaniment There is little tendency to a low basal metabolic rate On the contrary Newburgh (1942) has pointed out that obese persons with their larger surface area produce more heat than those of normal weight The

specific dynamic action of proteins and other foodstuffs is not abnormal in the obese Demonstrable endocrine upsets are a relatively infrequent accompaniment of the more severe forms of obesity Myxœdema is not so often accompanied by obesity as is often believed Plummer (1010) found increased weight in only 60 per cent of a series of 200 cases of myxœdema and in most of these it was mainly due to water retention Clearly diagnosable forms of hypopituitarism though not necessarily associated with loss of weight rarely show appreciable gain In Cushing s basophilic syndrome the obesity is mild being less than at first sight appears owing to the false impression produced by the prominent chest cage and the shortening of the spine resulting from the associated osteoporosis No evidence of hypopituitarism can be obtained in the great majority of cases of obesity It is probable that the hypothalamus can play a part in the production of obesity Damage to the hypothalamus from chronic encephalitis is sometimes accompanied by considerable gain in weight though loss is more usual (Greene 1939) Encephalitis however is a rare cause of obesity

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even less Newburgh believes that in such cases the failure is only temporary and is usually due to water retention

Diets suited to the individual can be constructed by making full use of vegetables fruit milk lean meat and eggs according to the food composition tables available in most text books An adequate intake of vitamins must be ensured Details of such diets are given by Newburgh in his review Newburgh considers that it is better to limit the diet sharply to a low figure, rather than to effect a gradual reduction in calorie intake Such a reduction is more readily tolerated if dexedrine be given in addition

Dexedrine in Obesity Benzedrine was first used for this purpose by Lesses and Myerson (1938) That benzedrine causes a deterioration of appetite had frequently been noticed since the early days of its use as a mental stimulant The nature of the action is still not entirely clear It has been shown that benzedrine relaxes the stomach and increases the tone of the pylorus thus producing a delay in the rate of emptying There is an increase in mental activity and a tendency to euphoria and these contribute by diverting the patient s attention from his appetite and by increasing his will power to persevere Albrecht (1944) confirmed the findings of Lesses and Myerson and by giving benzedrine alone without any dietary restriction at all obtained such an effect on the appetite that weight was frequently reduced in this way to normal He obtained an average loss of weight in 300 cases of four lbs per week and only one patient failed to lose weight while taking the drug Williams and colleagues (1948) compared several similar compounds and found dexedrine superior to benzedrine Dexedrine is now more generally used Although dexedrine without a diet produces steady weight loss it is probably better to combine from the first the use of dexedrine with an imposed dietary restriction and to use the period of reduced appetite to develop more suitable dietary habits If this is done the patient will not be encouraged to believe that the taking of the drug is more important than a change in his own dietary habits

The commencing dose should be 5 mgms three times a day combined with a diet of about 1,000 calories The dose of dexedrine may be increased gradually if necessary to a maximum of 30 mgms a day Serious adverse effects from the drug are infrequent Trouble from insomnia is less frequent than might be anticipated it may be controlled by giving the dexedrine during the earlier part of the day and by a small dose of phenobarbitone at night Dexedrine so used has no appreciable effect on the metabolic rate and it rarely causes a serious rise in blood pressure Addiction to the drug when used in obesity appears so far not to have been recorded Albrecht (1944) gives as the main symptoms encountered from the use of benzedrine

loss of appetite 88 per cent dryness of the mouth 50 per cent increased psychomotor activity 48 per cent and headache usually mild 32 per cent Insomnia occurred in only four per cent The effects of dexedrine are similar Edwards and Swyer (1950) have recently *shown that weight loss is significantly more rapid under diet and* dexedrine combined than it is when diet alone is used It is particularly important in using such a mode of treatment to stress throughout the importance of the change in dietary habits and to make it clear to the patient that the main purpose of the dexedrine is to facilitate this change

The contraindications to the use of dexedrine in view of the side effects which may occur are undue excitability or insomnia and coronary or other cardiac conditions in which vasoconstrictors are undesirable

Exercise in Obesity Newburgh (1942) has pointed out that exercise is a much harder way of reducing weight than dieting A man of 250 lbs will need to climb 20 flights of stairs to rid himself of the energy of one slice of bread and a walk of 36 miles will theoretically be required to burn off one pound of adipose tissue Little effect should *therefore be expected from an increase in exercise*

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CHAPTER XI

PSYCHOSOMATIC MEDICINE

by

HENRY MILLER and ROBERT ORTON

Physiological considerations The constitutional factor Psychopathology Psychosomatic diagnosis and therapy The cardiovascular system Asthma Anorexia nervosa Psychosomatic factors in skin diseases

PSYCHOSOMATIC medicine is not a new speciality but an approach to medicine and surgery which implies attention to the emotional as well as the physical aspects of all diseases In general it may be defined as the field of application of psychiatry to general medicine studying particularly bodily changes resulting from emotional disturbance Increasing interest in the subject can be recognised as one aspect of a move away from a mechanistic view point and towards a more humanistic and biological orientation of medicine generally studying the patient as a whole person and not merely as a collection of diseased organs

The historical reasons for this development are not far to seek Nineteenth century medicine was dominated by Virchow s cellular pathology with its essentially structural concept of disease and by a bacteriological era which regarded diseases as the predictable effects of accidental infections in which the role of the host was largely passive Such a pathology dealt with disease states rather than disease processes and had its counterpart in therapeutic nihilism

During the present century however pathology has become increasingly dynamic in its outlook recognising most diseases as vital reactions to injury and many gross structural changes as the result rather than the cause of disturbed function In medicine also, a similar stress on processes rather than conditions has resulted from studies in biochemistry immunology and allergy

Meanwhile psychiatry has undergone broadly similar changes Freud attempted to produce a biologically orientated psychology and increased our understanding of the psychogenic factors in neurosis and to some extent of the mental mechanisms observed in normal *behaviour* Psychiatry also has become increasingly dynamic and able to advance from its previous preoccupation with description and classification while studies in the physiology of emotion conditioned reflexes and neuro and electro physiology have contributed to rapid progress

Already psychiatry has contributed concepts of great value to clinical medicine First the principle of *body mind* or *psychosomatic unity* Unlike the philosopher the physician has little difficulty in accepting that psychological and somatic phenomena take place in the same biological system and are probably two aspects of the same process Secondary to this is the realisation that the sharp separation of diseases into 'organic and functional is no longer acceptable the basis for such a division lying in a contemporary medical attitude and not within the animal at all (Draper 1944) *The either or concept is discarded* and the biochemistry of the emotionally determined anxiety state *becomes equally with psychological aspects of peptic* ulcer a valid subject for scientific enquiry From this follows also the applicability to general medicine of the psychiatric principle of *multiple ætiology* with an attempt to assess the relative ætiological contributions of a constellation of genetic traumatic toxi infective and emotional factors to each disease process and in each case

The very word psychosomatic implies duality and is in fact a most unsatisfactory term Kanner (1948) states that by psychosomatic medicine is really meant an effort to study with modern medical and psychiatric methods individual human beings as they are feel and relate themselves to their world before and when they get sick while they suffer and when they are helped to improve This definition comprises virtually the whole of medicine of which one could rightly say that psychiatry is a part There will still remain however a particular group of sick people the approach to whom will be largely psychological and the care of whom *will remain the particular* task of the psychiatrist Some patients will require the ministrations of both the general physician and the psychiatrist and it may be that the label psychosomatic will remain attached to such cases

Psychosomatic medicine covers a considerable field of disease lying between the frank psychoses and psychoneuroses on the one hand and on the other hand the comparable mass of pathological conditions in which emotional factors appear to play a relatively unimportant or purely secondary part *It deals less* with the symbolic physical symptomatology of the psychoses and hysterical conversion symptoms

than with the somatic accompaniments *of states of abnormally pro* longed anxiety and tension Somatic symptoms in the first two categories are not accompanied by physiological changes peripherally and have a physical basis only in so far as all mental events are accompanied by physiological activity in the cerebral cortex In the anxiety reaction however, the symptoms are physically mediated, and recognisably related to normal physiological responses on emotional stimulation

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PHYSIOLOGICAL CONSIDERATIONS

Many clinical and experimental observations comprehensively reviewed by Wittkower (1935) demonstrate the frequency with which physical events in the healthy or diseased body are produced by emotional stimuli particularly when such stimuli are of importance *in the instinctual life of the subject*

Vasomotor changes are amongst the most frequent and are exemplified by blushing or blanching of the skin with superficial temperature changes Similar alterations in visceral blood flow may produce syncope and pathological analogues are found in emotionally provoked paroxysms of Raynaud s syndrome and angina pectoris Increased cardiac output and dilatation tachycardia with a shortened atrio ventricular conduction time transient hypertension polycythæmia and leucocytosis have also been demonstrated in experimentally *induced emotional disturbances* Involvement of skeletal musculature in emotional states is evident in everyday observations of facial expression and in the increased tone tremor and actual muscular weakness which may accompany excitement Nervous diarrhœa frequency of micturition and occasional incontinence as well as some emotionally provoked asthmatic attacks reveal the implication of smooth muscle while the effect of emotion on glandular function is seen in the dry mouth and cold sweat of fear, in the gastric hypersecretion which accompanies hyperæmia and hypermotility following periods of prolonged emotional tension and in the vagally mediated insulin secretion of the cat confronted by a barking dog

The physiological mechanisms underlying such emotionally induced changes are partly understood and involve both viscera and skeletal

musculature Emotions are of course conscious feelings excited by afferent stimuli which may produce an immediate or delayed response and in which activity of the cerebral cortex particularly perhaps of the frontal areas is an integral part The cortex appears through cortico thalamic connections to modify the more stereotyped functions of reflex emotional expression which are localised with crude sensibility and primitive feeling tone in the neighbourhood of the thalamus The efferent impulses controlling visceral and somatic emotional expression descend from the thalamic region close to the walls of the third ventricle and here the hypothalamus plays an important effector role the integrity of its posterior nucleus in particular being essential to the complete rage reaction of the thalamic animal In the hypothalamus the emotional pathways are brought into close relation with centres playing a vital part in regulation of shivering water carbohydrate and probably fat metabolism blood pressure and heart rate gastrointestinal motility sleep and sexual functions From this level fibres pass down in the tegmentum of the midbrain lying mesially and separate from the pyramidal tracts into the pons and spinal cord Those to the skeletal musculature pass out of the final common path while visceral impulses are distributed through the ramifications of the autonomic system where sympathetic action is reinforced and prolonged by the adrenals The physical components of emotional expression do not however result solely from sympathetic activity but represent the product of simultaneous activation of sympathetic and parasympathetic responses evident in some of the examples already quoted

A feature of clinical significance is that while physiological response is often relatively non specific as between emotions it is frequently strikingly specific in the individual subject The response to anxiety is not always purely sympathetic but is a general autonomic disturbance In some patients anxiety provokes tachycardia and a rise in blood pressure In others the blood pressure falls and in such subjects fainting attacks may thus form part of the somatic response to anxiety In the individual patient however the blood pressure will always exhibit the same response to anxiety whether it be rise or fall A similarly variable response to emotion occurs in functional dyspepsia in that some patients tend to have gastric hypersecretion and hyper motility whereas others show the opposite response leading to a low acid curve Again the patients respond variably but the response is consistent within the individual Patients also tend to show a more marked somatic response in one or other system of the body In response to anxiety some patients tend always to show changes in the cardiovascular system whereas others show changes in gastric function There is some evidence that constitutional factors play a

than with the somatic accompaniments of states of abnormally prolonged anxiety and tension Somatic symptoms in the first two categories are not accompanied by physiological changes peripherally and have a physical basis only in so far as all mental events are accompanied by physiological activity in the cerebral cortex In the anxiety reaction, however, the symptoms are physically mediated and recognisably related to normal physiological responses on emotional stimulation

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The physiological mechanisms underlying such emotionally induced changes are partly understood and involve both viscera and skeletal

predisposing to particular emotional situations Modern work suggests that differences in physique vary between two extremes which can be plotted on a normal curve of distribution At one end are the so called asthenic or leptosomatic individuals whereas at the other end are the pyknic or thick set individuals The majority of people lie between these two extremes and this accounts for the difficulty in correlating physique with both personality types and particular types of psychiatric reaction At the extremes however the correlation is high Present evidence does suggest a very definite relationship between physical constitution and personality

Flanders Dunbar is a pioneer in this field and the results of 12 years large scale research at the Presbyterian hospital New York have recently been summarised (Dunbar 1943) This author adduces evidence based on thorough study of serial general hospital patients from both medical and psychiatric aspects for several significant psychosomatic correlations The fracture cases originally selected as control material for example turned out themselves to have many personality characteristics in common being typically accident prone impulsive adventurous and given to immediate action in striking contrast with the highly developed control of emotional life and behaviour restless ambition strenuous independence and sustained drive shown by a high proportion of the patients with coronary disease

When one reads the personality vignettes of patients suffering from various psychosomatic disorders one is struck quite frequently by their similarity the differences are indeed very finely drawn and at times so finely drawn as to defy separation Alvarez states that patients with peptic ulcer are often go getters Mittelmann (1933) and Conrad (1934) state that patients with exophthalmic goitre fall into three groups the third group being described as aggressive and hard driving with a high level of activity It would appear difficult to differentiate between an individual who is aggressive and hard driving with a high level of activity and a go getter This criticism of the correlation of personality with psychosomatic disorders is a very real one and it seems likely that a group of individuals is prone to psychosomatic disorders but that which particular disorder they develop depends on constitution Attempts to correlate the particular illness with a characteristic personality or with a special emotional situation are generally unconvincing

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part in determining the bodily system most disturbed by emotional factors

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CONSTITUTIONAL FACTORS

Physical aspects of constitution or "diathesis" have been dealt with by Eppinger and Hess (1917) with their concepts of vagotonia and sympatheticotonia, by Kretschmer (1925) who correlated psychiatric reaction type and physique by Sheldon (1942) who has greatly expanded Kretschmer's hypothesis and by Bauer (1943) who has attempted to assess the influence of genetic endocrine and 'abiotrophic' factors in modifying disease picture in different individuals and families In less speculative fields Draper (1944) has confirmed by carefully controlled anthropometric methods some common clinical impressions that liability to such diseases as peptic ulcer and cholecystitis is in some way related to physique These results are of great interest but their biological significance is not yet clear

In the psychosomatic field attempts have been made by psychiatric study of medical patients to correlate liability to various organic diseases with basic personality types In this connection it should be emphasised that personality implies the dynamic resultant of both genetic and environmental factors The difficulties inherent in such investigations and particularly in the provision of adequate controls are evident while over zealous propagandists have gone far beyond the facts in ready attribution of ætiological significance to their psychiatric findings The psychiatric history itself for example reveals to the investigator whether he is dealing with a case or a control relevant data are often unearthed with difficulty and the case formulation is bound to show a degree of subjective colouring The personality assessment too may be clear enough from a full case history but does not lend itself easily to reduction to unitary characteristics nor to convincing classification for comparative purposes The delicate variations analysed can rarely permit of statistical evaluation, while even in the presence of a significant correlation an ætiological relation between personality type and disease cannot be unreservedly accepted personality influences way of life and this introduces complicating environmental and occupational factors as well as

predisposing to particular emotional situations Modern work suggests that differences in physique vary between two extremes which can be plotted on a normal curve of distribution At one end are the so called asthenic or leptosomatic individuals whereas at the other end are the pyknic or thick set individuals The majority of people lie between these two extremes and this accounts for the difficulty in correlating physique with both personality types and particular type of psychiatric reaction At the extremes however the correlation is high Present evidence does suggest a very definite relationship between physical constitution and personality

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PSYCHOPATHOLOGY

While our understanding of mental events lags far behind our knowledge of the mechanisms by which these produce their physical effects psychological phenomena cannot be adequately discussed in terms of physiological analogy, and to ignore the emotional dynamics of neurosis or psychosomatic illness leads therapeutically to a purely symptomatic approach, as unacceptable here as in other fields of medicine

Psychopathology is an unsuitable subject for brief presentation The interested reader will find in the references listed below, starting points for further study and the elicitation of full case histories from 100 neurotic patients will at least modify undue initial scepticism the unconscious illustration of psychopathological concepts from the lips of an untutored patient carrying more conviction than text book presentations

A simple grouping of the conditions in which emotional factors play a part in producing illness may help understanding —

(a) *Patients who are anxious but have a full conscious awareness of both the anxiety and its sources* This anxiety may provoke somatic symptoms e g dyspepsia but the patients recognise the relationship of the dyspepsia to the anxiety Such individuals are not strictly speaking neurotic but are merely showing an excessive somatic disturbance to the normal anxieties of everyday life

(b) *Patients who are anxious and have a full conscious awareness of the anxiety and its sources but do not relate somatic symptoms to the anxiety itself* E g the individual has dyspeptic symptoms but does not recognise their relationship to anxiety These patients are in a way neurotic in that they dissociate cause and effect Nevertheless they remain relatively easy to treat and usually it is not difficult to help them to see cause and effect

(c) *Patients who are anxious but in whom the cause of the anxiety is repressed* These patients develop symptoms and are usually blind to the fact that the symptoms are provoked by anxiety and they are also equally blind to the facts which are provoking the anxiety These patients may be described as more severely neurotic than Group (b) and are likely to require skilled psychiatric help

(d) *Patients in whom not only is the cause of the anxiety repressed but the anxiety is also dissociated* These patients are hysterics They do not develop true somatic disturbance secondary to anxiety because the anxiety is dissipated by various mental mechanisms These patients present an entirely psychiatric problem

Groups (*a*) and (*b*) are very definitely psychosomatic and can usually be handled by the general physician without psychiatric assistance Patients in Group (*c*) frequently have a psychosomatic disorder but are likely to require psychiatric as well as general medical assistance Group (*d*) is strictly speaking not psychosomatic but entirely psychiatric

PSYCHOSOMATIC DIAGNOSIS AND THERAPY

The chief instrument of psychosomatic investigation is the clinical history recorded in the patient s own words and covering as fully as possible both general medical and psychiatric aspects of the case The medical history is chiefly directed towards an evaluation of physical factors in ætiology and symptomatology and in this connection it must be stressed that even in cases where psychological factors are ætiologically significant they may be neither the sole nor the most important contributing cause The psychiatric history has two objects The first is to obtain a clear picture of the patient as a person—a *personality assessment* Irrespective of any possible ætiological significance this is of immediate importance in the proper management of the case The second object is to determine the existing emotional situation and the *present psychiatric reaction* which in these cases will usually reveal the pattern of one of the familiar psychoneuroses of anxiety hysterical or obsessional type but it must not be forgotten that a psychotic illness also may provoke a psychosomatic disorder It is the mild psychosis which is so frequently missed and which frequently *gives rise to difficulty in diagnosis*

The psychiatric history aims then at a detailed historical account of the patient s life story with particular attention to family background infancy school and work records and adjustments to the successive crises of normal development and socialisation Neurotic traits and symptoms attitudes to illness and the habit of using medical symptoms to escape from difficult situations are specially enquired for Adjacent chronological tables of life situation and medical symptomatology will often reveal a previously unrecognised relation between obscure *medical complaints and periods of emotional stress*

Given adequate time it is usually possible to secure a great deal of information without recourse to special techniques Above all the patient should be encouraged to talk freely about himself without interruption such mental catharsis has a definite therapeutic value while his omissions evasions and denials often yield valuable clues as to the nature of worries he refuses to admit

Therapy *Treatment begins with the taking of a full history* and an equally thorough examination This should be followed by a

clear and definite statement of the position as the physician sees it In the absence of structural disease (e g in cardiac neurosis), the patient should be firmly reassured on this point, and in mild cases this may be all that is required Many such patients, however, must be helped by discussion with the physician to recognise the nature of their personal problems, and to deal with them The use of drugs or other physical methods of treatment in psychogenic disturbances of function is entirely logical provided that wherever possible emotional factors are investigated and treated simultaneously that the essentially symptomatic nature of such physical treatment is clear to patient and doctor and that the power of medical suggestion is carefully considered in any attempted assessment of therapeutic results Where there is a structural "organic" component in the patient s condition the importance of a combined approach is even more evident Here it must be recalled that psychological factors may still be responsible for the major part of the patient s actual disability and that these may be the factors most susceptible to treatment Such a situation is often found for example in early heart disease and hypertension where circulatory symptoms out of proportion to physical findings not infrequently indicate a coincident and remediable anxiety state

Finally and although results in this field are at least as good as in other branches of medicine some psychosomatic disorders are incurable either because the patient is too unintelligent or too inadequate to co operate or because he clings to his symptoms as the only possible answer to an insoluble situation Trudeau s aphorism ' to cure sometimes to relieve often to comfort always is particularly relevant here and many such patients make a social adjustment with the help of an understanding practitioner

REFERENCE

DUNBAR F (1943) Psychosomatic diagnosis New York

THE CARDIOVASCULAR SYSTEM

Psychoneurosis with effort intolerance (*Cardiovascular Neurosis Effort Syndrome Da Costa s Syndrome Neurocirculatory Asthenia*) As during all wars since Da Costa s description in 1871 considerable attention has recently been focused on this condition and the excellent reviews of Fraser (1940) Wood (1941) and Dunn (1942) typify the reorientation that has taken place since 1914–1918 During the first world war the physical phenomena of the condition were analysed in a considerable cardiological literature but the contemporary scotoma for emotional factors in ætiology and the stressing of occasional cases in which a similar symptomatology was associated with early organic heart disease led to the complete neglect of such early papers as adduced evidence for a psychogenic basis

(Oppenheimer and Rothschild 1918 Cohn 1919) Paul Wood s Coulstonian lectures (1941) are of particular interest in that besides presenting a comprehensive review of the literature and many experimental observations clarifying the mechanisms of symptom production they describe the steps by which the author reached his conclusions on the emotional basis of the condition

The fairly general acceptance of this syndrome as a typical psychosomatic disorder the autonomic expression of a clinically demonstrable psychoneurosis usually of chronic anxiety type rests not only on the absence of a demonstrable structural basis or organic sequelæ but also on certain positive features First there is nothing specifically military about the condition in most army cases its onset preceded service and it is common in civil life amongst women and children The evidence suggests a higher incidence in emotional races and clinically the condition is usually associated with evidence of predisposition to neurosis in both the personal and family histories and with personal inadequacy characterised particularly by abnormal physical timidity A careful history reveals that the characteristic cardiac manifestations are but a part of a more extensive and multiple symptomatology which usually includes cold blue extremities rapid irregular breathing sighing sweating of emotional distribution tremor dizziness headaches and a dry mouth With their concomitant physical signs these symptoms reveal a widespread autonomic disturbance of central origin and as in the case of the cardiac symptoms themselves the whole picture resembles much more closely the normal physiological response to fear than an over response to exertion (Wood 1941) It is worth noting also that the relation of symptoms to effort is highly selective and markedly influenced by the patient s emotional attitude to the exertion concerned and that early organic heart disease is by contrast usually symptomless

The psychological background has been excellently described by Wood and his findings accord with general experience Typically a nervous timid and over protected boy is seized with panic during exertion usually on the football field or while swimming The physical symptoms of acute fear are misinterpreted by the child and his mother and all too often by the doctor as an abnormal response to the coincident physical effort and attention is directed to the heart In the naturally apprehensive subject repetition of such a frightening experience on a few occasions is in any case liable to establish it as a conditioned response to any exertion even when this is undertaken under conditions not in themselves productive of fear Such a development is facilitated by medically induced anxiety about heart disease and possible sudden death and by the atmosphere of intensified over protection which ensues In later years these patients

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generally adopt a mode of life which makes few physical demands but when they have to leave the office for the army both the physical effort and the fear producing situations involved usually lead to an increasing incapacity, in the genesis of which a hysterical escape mechanism is also often clearly evident

The treatment of the established condition is by repeated reassurance careful explanation adapted to the level of the patient s intelligence and graduated exercise As in all such conditions prognosis depends more on the patient s personality than on the symptomatology but of longstanding cases not more than one in four can be completely relieved of symptoms and in the majority the most that can be done is to minimise disability and invalidism through patient re education Of all neuroses this is the one in which iatrogenesis (production by the physician) is most marked and the prophylactic implications are evident

Emotional Factors in Organic Cardiovascular Disease That emotional factors can influence established heart disease is apparent in the classical instance of emotionally induced paroxysms of angina pectoris and in the less familiar but well authenticated provocation of coronary occlusion under similar circumstances There is objective evidence also that emotional changes can alter cardiac function Mainzer and Krause (1940) describe well controlled observations in which electrocardiographic changes of coronary insufficiency type were produced by fear in this case pre operative and they comment on the possible operation of a similar mechanism in sudden death during early anæsthesia in a frightened patient It is of interest that similar E C G changes (inversion of T_1 and T) more persistent but still reversible have been described in *effort syndrome* (Graybiel and White, 1935 Merritt 1944)

It is less generally appreciated that symptoms out of proportion to the objective organic disability in early valvular disease or minor congenital anomalies are often due to the existence of a coincident anxiety state in which over concern about the heart is often an important feature and which may be treatable with marked improvement in the cardiac and general symptomatology In more severe valvular disease emotional disturbance may be followed by the onset or exacerbation of congestive failure and in these cases Wolfe (1936) has suggested that autonomically induced cardiac over action such as would produce the symptoms of cardiac neurosis in the healthy heart provokes failure in the presence of an organic lesion In hyper tensive cardiovascular disease Weiss (1940) has shown that emotional situations can induce exacerbations of hypertension encephalopathic crises pulmonary œdema and intracranial hæmorrhage

Essential Hypertension We have seen that emotional causes

can produce disabling cardiovascular symptoms without irreversible structural change and that they can also influence unfavourably the progress of established organic heart disease Whether similar influences also play any part in the actual ætiology of organic cardio vascular disease comparable for example with that for which there is evidence in the genesis of peptic ulcer remains an open question Interesting contributions to this subject with particular reference to essential hypertension have been made by Alexander (1939) Weiss (1939 1940) and Dunbar (1943)

Vascular hypertension is predominantly a disease of occidental civilisation and the observation that it is both frequent and severe in the American but rare in the African negro indicates that cultural factors are intimately interwoven with the apparent heredofamilial tendency for which there is clear clinical evidence Constitutionally hypertension is significantly more frequent among the broad and obese than in slender subjects and is often associated with a family history both of cardiovascular disease and diabetes (Dunbar 1943) It is a condition of multiple ætiology and in a small minority of patients a pathological basis for the hypertension can be discovered (e g unilateral renal disease chronic pyelonephritis adrenal pheochromocytoma) while in the experimental animal a comparable condition can be produced by bilateral denervation of the carotid sinus subtotal nephrectomy irradiation of the kidneys Goldblatt clamps and the injection of pressor substance extracted from the ischæmic kidney In the vast majority of clinical cases however the primary ætiology is unknown and the most that can be said of pathogenesis is that the available clinical and pathological evidence suggests that the condition probably depends on circulatory changes in the kidney leading to increased production of pressor substances producing hypertension secondary to generalised vasoconstriction

Emotion and hypertension The influence of emotion on blood pressure is evident from the allowance always made for the emotional factor in individual blood pressure readings It is less generally appreciated that a more persistent elevation of diastolic as well as systolic pressure may occur in association with acute anxiety and tension states and may settle down when the affective symptoms are relieved by treatment The studies of Robinson and Brucer (1939) suggest that many of the patients in whom this phenomenon is observed may be potential hypertensives Certainly the similar fluctuations of pressure which are often found in early cases of essential hypertension lend support to the view that this condition is determined initially by disturbances of circulatory function rather than by the irreversible changes found at autopsy which represent to a considerable extent the result rather than the cause of the disease

Psychiatric studies of patients with essential hypertension (Alexander, 1939, Weiss, 1939, 1940, Binger *et al*, 1945, Dunbar 1943) have yielded singularly consistent results These authors have amplified traditional clinical observations and have described in greater detail the personality features common in patients with this disease It is generally agreed by these and other investigators that hypertensive patients frequently show signs of longstanding strain and chronic anxiety The similarity between the early symptoms of hypertension and those of psychoneuroses has often been noted and psychiatric studies show that neurotic symptoms particularly of obsessional compulsive type are common at an early stage of the illness, when they cannot be adequately accounted for by the physical effects of the disease and that such symptoms can often be successfully treated by psychological methods

Dunbar has shown that psychiatric studies of many of these patients reveal consistent personality traits evident in their pre hypertensive history and indeed throughout their lives They are characteristically hard driving, ambitious dominant characters with a strict control of their emotional life only occasionally released in an explosive manner in aggressive fits of temper or in periodic debauchery at times of stress The hypertensive patient tends to smoke and drink too much and the tenseness which is the keynote of his personality is often evident in a tendency to spasm in the voluntary and smooth musculature The onset of hypertensive symptoms often coincides with a long period of mounting stress and occurs under circumstances which in less emotionally inhibited subjects might be expected to give rise to a full blown neurosis The patient's attitude to his illness may follow one of several patterns He may obstinately ignore it, or may show a combination of anxiety and actual relief at the excuse which the illness affords for not achieving his long term objectives Analytic observers find *suppressed aggression* a striking personality trait in many of these patients and Alexander (1939) in a stimulating paper formulates a tentative hypothesis on the relation between the emotional background and the hypertension He suggests that in subjects of a particular physical and mental constitutional make up, aggressive impulses suppressed by personal and social inhibitions may give rise to emotional tensions and autonomic disturbances which affect the physiological control of blood pressure leading to hypertension and secondary organic changes in the vasculature In this connection Weiss and English (1943) mention the possibility that central nervous factors might conceivably operate by altering the circulatory dynamics of the kidney Some such mechanism has been suspected on clinical grounds to account for the well authenticated occurrence of emotionally induced diuresis and anuria and its existence has recently been

demonstrated by the experimental observations of Trueta *et al* (1946) These workers have shown that in experimental animals stimulation of the central end of the divided sciatic nerve can produce a shunt in the intra renal circulation with a sub cortical short circuit and cortical ischæmia revealed by radiography and vital staining These important observations may throw light both on the pathogenesis of essential hypertension and on the mechanisms of therapeutic sympathectomy

If as seem possible emotional factors acting in some such way can play a part in the causation of certain cases of essential hypertension some important reservations should be borne in mind First the constitutional and possibly hereditary background seems to provide an invariable physical basis for the development Secondly while in some cases the activating factor may be psychosomatic it is certain that in others the hypertension depends on primarily physical disease in the kidney or elsewhere Thirdly psychiatric treatment is likely to be curative if at all only in the earliest stages of the disease before irreversible structural changes have supervened that is when the condition is still a psychoneurosis in a subject constitutionally pre disposed to hypertension

These observations are however not without value in the manage ment of established hypertension They indicate the need for taking emotional and personality factors into account in each case for treating the patient rather than the blood pressure and for helping him to make the most of the creative outlets still open to him despite his disability Whether primary or not the psychological factor is certainly of importance in many cases and it is at any rate more accessible to treatment than the constitutional basis

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ASTHMA

It is at present fashionable to regard asthma as primarily a psycho somatic illness It demonstrates, however all the gradations between a truly somatic and a truly psychogenic disorder At one end of the scale is the psychiatrically stable subject devoid of demonstrable neurotic trends but with a marked family history of allergic manifesta tions At the other is the patient generally regarded as asthmatic, but in fact displaying attacks of hysterical tachypnœa Many asth matic patients suffer also from psychological disturbances but whether such disturbance is causal coincident or resultant is often very difficult to decide A still larger proportion of asthmatics develop their attacks in response to emotional stress but they are often well aware of this and not really neurotic at all They should be helped by wise general management to avoid such stress as far as possible deep psychotherapy is not necessary Finally in some cases asthma serves to facilitate escape from responsibility, but this is usually merely a secondary gain from the illness and an important complicating rather than a causal factor

An elaborate analytic study of psychogenic factors in bronchial asthma has been made by the Chicago Institute for Psychoanalysis (French and Alexander 1941) It is said by these workers that throughout the lives of patients subject to psychogenic asthma there runs an undercurrent of fear of estrangement from the mother which is more or less deeply repressed The cause of such fear is considered to be the patient s own forbidden impulses which he thinks will offend the mother Psychotherapeutic unearthing and confession of these impulses is said to relieve the asthmatic if however he is afraid to confess an asthmatic attack is likely to be precipitated A more detailed account of psychotherapy in asthma is given by French and Johnson (1948) There is little evidence however of a therapeutically successful psychoanalytic approach to asthma except in a very few cases

In addition to the ordinary neurotic mechanisms which provoke asthma it is important to mention that asthma may be provoked by a psychosis in particular by agitated melancholia The agitation may be so severe as to provoke a very definite asthma and the patient

may present as a case of asthma although the real diagnosis may be melancholia Such patients respond to convulsive therapy and as their agitation disappears so does their asthma This type of case is perhaps most frequently seen in the involutional period and such patients usually have no family or previous history of asthma They frequently struggle with their asthma for one to three years and as the melancholia remits so does the asthma often never to return again In these patients the depression of mood is often regarded as secondary to the asthma but a detailed history will show the usual rhythm of melancholia in that the patient tends to be worse on rising and to improve as the day wears on Sleep is disturbed the patient waking frequently through the night agitated and also asthmatic

A purely psychological approach is rarely of benefit in asthma and most patients are best treated by a general physician An appreciation that emotional strain exacerbates the disorder will enable the general physician to enlarge the scope of his treatment to include the patient s life as well as his chest

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ANOREXIA NERVOSA

Anorexia nervosa is a disease in which structural changes, endocrine dysfunction and death can follow a primarily emotional illness The clinical features have been excellently reviewed by Ryle (1936) who drew attention to the high incidence in private patients the characteristically difficult personality with remarkable retention of energy despite extreme emaciation hirsutism bradycardia and hypotension the absence of avitaminoses and the return of menses as a sign of established recovery The basic metabolic rate may be as low as minus 40 per cent and the low glucose tolerance curve is probably due to delayed absorption being normal when sugar is given intravenously Sheldon (1937) has described the endocrine picture as a functional Simmond s disease—a pituitary black out of psychological origin

The psychiatric background of the disease has recently been more fully investigated The diagnostic symptom may arise in the course of various psychiatric syndromes and there seems to be every gradation between the loss of appetite accompanying anxiety reactions and the complete refusal of food seen in some severe psychoses Some of the milder cases are in fact suffering from anxiety states in others the refusal of food is part of a hysterical state or an obsessional syndrome while many are schizoid personalities and even latent schizophrenics who may deteriorate to a frank psychosis True anorexia

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ASTHMA

It is at present fashionable to regard asthma as primarily a psychosomatic illness It demonstrates however all the gradations between a truly somatic and a truly psychogenic disorder At one end of the scale is the psychiatrically stable subject devoid of demonstrable neurotic trends but with a marked family history of allergic manifestations At the other is the patient generally regarded as asthmatic but in fact displaying attacks of hysterical tachypnoea Many asthmatic patients suffer also from psychological disturbances but whether such disturbance is causal coincident or resultant is often very difficult to decide A still larger proportion of asthmatics develop their attacks in response to emotional stress but they are often well aware of this and not really neurotic at all They should be helped by wise general management to avoid such stress as far as possible deep psychotherapy is not necessary Finally in some cases asthma serves to facilitate escape from responsibility but this is usually merely a secondary gain from the illness and an important complicating rather than a causal factor

An elaborate analytic study of psychogenic factors in bronchial asthma has been made by the Chicago Institute for Psychoanalysis (French and Alexander 1941) It is said by these workers that throughout the lives of patients subject to psychogenic asthma there runs an undercurrent of fear of estrangement from the mother which is more or less deeply repressed The cause of such fear is considered to be the patient s own forbidden impulses which he thinks will offend the mother Psychotherapeutic unearthing and confession of these impulses is said to relieve the asthmatic if however he is afraid to confess an asthmatic attack is likely to be precipitated A more detailed account of psychotherapy in asthma is given by French and Johnson (1948) There is little evidence however of a therapeutically successful psychoanalytic approach to asthma except in a very few cases

In addition to the ordinary neurotic mechanisms which provoke asthma it is important to mention that asthma may be provoked by a psychosis in particular by agitated melancholia The agitation may be so severe as to provoke a very definite asthma and the patient

evidence rather than direct questioning until the patient's confidence is gained Occupational therapy may help in the re-education and socialisation which are the basis of treatment Although many patients spontaneously overcome this crisis in their development towards maturity without such help extended psychotherapy has a definite place in the treatment of the more intelligent and co-operative patients

Anterior pituitary and œstrogenic hormones thyroid and insulin are of doubtful value Hemphill (1944) has described remarkable recovery of appetite 17 ketosteroid output, and clinical state immediately following prefrontal leucotomy in a severely obsessional patient with anorexia and emaciation but the field for such treatment in this disease must be small

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PSYCHOSOMATIC FACTORS IN SKIN DISEASES

Multiple causation is nowhere better illustrated than in dermatoses Hysterical self infliction and the relation of parasitic infections to subnormal intelligence or of fungus disease to emotional hyper hydrosis are gross examples of indirectly operating psychiatric factors in ætiology but dermatologists increasingly recognise the importance of a more direct emotional element particularly in many cases of urticaria hyperhydrosis the asthma prurigo complex, and pruritus The subject has been fully reviewed by Stokes and Beerman (1940) and its relation to the autonomic nervous system by Rothman (1945) while Hellier (1944) and MacKenna (1944) have contributed excellent clinical papers based on military dermatological experience Amongst the physiological mechanisms relating skin reactions to emotional disturbances are psychogenic vasomotor phenomena such as blushing emotional hyperhydrosis which chiefly involves the apocrine glands of *palms soles and axillæ and is probably mediated through a distinct autonomic pathway* and emotionally provoked urticaria attributed on experimental grounds by Grant *et al* (1936) to liberation of a histamine-like substance in skin cells following release of acetylcholine at peripheral nerve-endings

MacKenna (1944) has elaborated the stimulating hypothesis that liability to particular dermatoses can be correlated with personality

nervosa is *most frequently seen in adolescent females* Anorexia nervosa in the male or in either sex occurring later in life, is usually the presenting *symptom of a fairly serious disorder nearly always* an early psychosis In young patients the psychosis is nearly always schizophrenic, but in *older patients quite frequently depressive* The possibility of an organic psychosis however should not be forgotten and a patient with cerebral metastases *may present as anorexia* nervosa

In the typical disorder, a family history of nervous breakdowns, abdominal diseases, gastrointestinal preoccupation and hypochondriasis and a personal past history of feeding difficulties are common The family situation is often abnormal Ryle comments on the occurrence of a curious combination of excessive devotion and wilful disobedience to the mother and conflicts between an immature overdependence and the impulse to break away seem to be at the root of this attitude In practically all cases the personality has been markedly abnormal before the onset of the illness which often follows a period of social and sexual maladjustment at puberty Many of these patients are odd, idealistic immature seclusive and reluctant to grow up with a restricted appetite for life as well as for food Faulty sexual attitudes are almost universal the patient repudiating sex, being often afraid of men and becoming distressed when the subject is discussed The rarity of cases in married women is notable while to some subjects the disease seems to be an excuse to ward off contacts with the opposite sex or to break off a reluctantly contracted engagement Many such *subjects have ill informed fears and fantasies about pregnancy* associated with feelings of guilt and urges to self punishment In some way *they seem to identify eating with sex and impregnation* and in many there is either a true complex determined fear of food or an ascetic pride in overcoming hunger rather than actual loss of appetite

Treatment No case is hopeless and prognosis depends more on personality than physical state Most cases recover

Prolonged institutional treatment away from the family and in a single room is usually advisable Tuberculosis or other infection excluded, the position must be clearly stated to patient and relatives Meticulous nursing supervision of the graduated normal diet immediately prescribed is essential to counter the patients frequent and elaborate subterfuge to avoid taking food Tube feeding should be a last resort as it may provoke suicide *The psychiatric approach is* difficult as many patients are hostile and resistant while most are unduly reserved and *reticent They will sometimes* eat their way out of hospital rather than reveal the emotional background to their illness *The physical* measures outlined above come first the psychiatric picture being built up in the first instance from collateral

According to this author the typical eruption of the hysteric is dermatitis artefacta, while prurigo, lichenification, pruritus ani, and dermatitis medicamentosa occur especially in obsessional subjects Rosacea pompholyx and disturbances of sweating are often associated with anxiety states and exhibitionism and immaturity characterise many patients with exudative dermatoses In the case of rosacea such a relationship has gained wide acceptance This condition has been described as a "chronic blush" and is frequently associated with prolonged anxiety reactions in abnormal personalities The typical patient is an unmarried woman in early middle life shy, retiring socially ill adjusted, morbidly self conscious, and unusually prone to feelings of guilt and shame The mechanism of the condition (e g its relation to histamine and the role of physical factors in ætiology) are not clearly understood but it is certain that onset and exacerbations are often closely related to emotional stress

That pruritus can be purely psychogenic is clear from the reactions of a class of students to whom a lousy head is demonstrated but the role of psychiatric factors in pruritus ani is less clear There is considerable evidence in favour of a relation to obsessional tendencies and in a few cases psychogenesis has been satisfactorily demonstrated A *pleasurable sexual component in itching and scratching* has been noted by many observers, and occasionally pruritus ani can be recognised as an immature substitutive sexual gratification sometimes with a background of homosexuality It is perhaps suggestive that prolonged narcosis and psychoanalysis have both yielded amelioration or cure when local treatment and more superficial psychiatric measures have failed the natural history of the condition often suggests a neurotic basis

Pruritus ani demonstrates again the neurotic basis of a somatic disturbance but it is less generally appreciated that a psychosis may similarly be responsible for a somatic upset Preoccupation with bowels is well known as a symptom of melancholia and pruritus ani is without doubt preoccupation with one s bowels When the patient also believes that his pruritus is due to some serious and "awful" disease one should become suspicious with regard to the possible diagnosis of a depressive illness It has often been mentioned that patients with pruritus ani may be driven to suicide Such patients are *nearly all suffering from melancholia* that diagnosis being missed due to the physician s preoccupation with the pruritus and his failure to assess the patient as a sick person

The occasional provocation of urticaria or angioneurotic œdema and the exacerbation of eczema or psoriasis by emotional disturbance are physiologically comprehensible as is the conception of hyperhydrosis of the feet as a manifestation of chronic fear following battle

experiences (Hellier 1944) The well authenticated cure of warts by suggestion and the activation of herpes simplex by emotion as well as by such agencies as coryza sunlight and menstruation (Rothman 1945) are however truly remarkable instances of infective processes directly influenced by psychological factors

Skin diseases like most psychosomatic disorders range from those which are purely psychogenic to those which appear to be purely somatic At one end of the scale is dermatitis artefacta and at the other herpes zoster The dermatologist is well able to treat most of the psychological disturbances found in patients suffering from skin diseases Only where the disorder appears to have a major psychological element is treatment by the psychiatrist required The psychological treatment of dermatological conditions is apt to be just as disappointing as a purely psychological therapeutic approach to most other psychosomatic disorders Nevertheless there have been encouraging reports on the psychological treatment of skin disorders and it has been claimed (Shorvon Rook and Wilkinson 1950) that abreactive techniques may benefit many patients with chronic skin diseases

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CONCLUSION

While the diseases reviewed in the present chapter serve to illustrate some of the methods and problems of psychosomatic medicine they are representative of a growing literature of comparable observation in other conditions Amongst the more important of these are studies of the psychiatric background in *coronary occlusion* (Arlow 1945) *accident proneness* (Dunbar 1943) *narcolepsy* (Langworthy and Betz 1944 Spiegel and Oberndorf 1946) *rheumatism* (Nissen and Spencer 1936 Halliday 1941 Flind and Barber 1945) *thyrotoxicosis* (Mittelmann 1933) *cardiospasm* (Weiss 1944) *diabetes* (Daniels 1939) and *migraine* (Wolff 1937)

Allport (1938) defines temperament in the following way —

Temperament refers to the characteristic phenomena of an individual s emotional nature including his susceptibility to

emotional stimulation, his prevailing mood and all peculiarities of fluctuation and intensity of mood these phenomena being regarded as dependent upon constitutional make up and therefore largely hereditary in origin "

Many of the descriptions of personality types found in various psychosomatic disorders are really descriptions of temperament which is widely regarded as constitutional We must be very careful to avoid describing what used to be termed 'diathesis" in fresh psychological terms which on closer analysis are really again descriptions of constitutional make up Although the literature of psychosomatic medicine is already extensive many lengthy descriptions of personality types must be regarded as merely new words which do not always lead anywhere either in understanding the disorder or in helping the patient The go getter is a go getter by temperament It is, however improbable that his go getting *causes* susceptibility to certain somatic diseases such susceptibility and such temperament *are each a part of his inherent make up*

In general it may be said that the concept of psychosomatic medicine represents a phase in the integration of psychiatry into the fabric of general medicine The term itself with its implied dichotomy is open to criticism and will probably be discarded as this integration becomes more complete When the emotional aspects of *all* illnesses are given adequate consideration in clinical practice and in medical education and when psychiatric assessment is as much a matter of course in the study of an obscure medical case as the employment of laboratory investigations, the term will be superfluous, for all medicine will then be psychosomatic

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CHAPTER XII

PHYSICAL METHODS OF TREATMENT IN PSYCHIATRY

by

ROBERT ORTON

Drugs in Psychiatry Alcoholism Dementia Paralytica Electric Convulsive Therapy Electronarcosis Insulin Coma Pre frontal Leucotomy Topectomy

This chapter is limited to physical methods of treatment not because psychological methods are despised or regarded as of no importance but because psychotherapy is usually very much a specialist occupation Most physicians realise that psychotherapy is the treatment of choice in the psychoneuroses but are somewhat bewildered by the various dramatic and slightly bizarre methods of physical treatment which have appeared in modern psychiatry Most methods of physical treatment in psychiatry are empirical Nevertheless some produce promising and occasionally dramatic improvement The conditions in which they are successful are frequently of unknown ætiology and the modus operandi of the treatments is equally unknown

Psychiatric schools of thought have become divided Freud tended to provoke a purely psychological approach and this single approach is the only one accepted by many psychiatrists Genetic factors however play a role in schizophrenia and various other mental disorders of unknown ætiology and this is well illustrated by Kallmann (1946) in his study of twins with schizophrenia If as seems likely there is physical basis in the constitution which plays a part in the development of such disorders as schizophrenia, it is reasonable to suppose that a purely psychological theory can only be a partial explanation, and that a psychological approach alone is likely to fail This statement of course applies equally to many of the so called

psychosomatic disorders where a combination of physical and psychological methods brings success and where a single approach is again likely to fail On the whole a purely psychological approach to schizophrenia or to manic depressive psychosis has been a failure whereas a physical approach has met at least with partial success

In psychiatry physical methods of treatment of major importance began in 1917 when Wagner Jauregg introduced malarial treatment in general paralysis This was followed by Klaesi (1922) who used barbiturates for prolonged narcosis Hypoglycæmic coma as a method of treatment was first reported by Sakel in 1933 This was soon followed by the introduction of chemically induced convulsive therapy in 1935 by von Meduna The present more favoured electric convulsive therapy was first demonstrated by Cerletti and Bini in 1938 Almost unnoticed at that time was the work of Moniz who in 1936 reported a surgical approach which was developed into the operation now known as a Pre frontal Leucotomy which has in turn given rise to the more recent operation of Topectomy The best general reviews of physical methods of treatment are those by Kalinowsky and Hoch (1946) and Sargant and Slater (1948)

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THE USE OF DRUGS IN PSYCHIATRY

Sedation The search for satisfactory sedatives continues particularly by the manufacturing chemists and most physicians must be somewhat bewildered by the large array which are offered Many of the older sedatives have now fallen into disuse some of them rightly so *e g* sulphonal and chloral hydrate are both apt to be capricious if given over a prolonged period of time The most popular group of sedatives are the barbituric acid derivatives and more phenobarbitone must be swallowed by the population than almost any other single drug The wholesale use of phenobarbitone has at least demonstrated that it is relatively safe even when administered for very long periods of time Barbitone (5 to 15 grains) and soluble barbitone (5 to 15 grains) are frequently used for insomnia Personal experience suggests that the absorption of these two drugs is apt to be very variable and much more reliable action is obtained with drugs in capsule form nembutal sodium amytal and seconal are all satisfactory quick acting hypnotics which are also fairly quickly metabolised the usual dosage for each being 1½ to 3 grains

A special enteric coating enables the absorption of the drug to be delayed for three to four hours Enseal seconal being such a drug

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of intravenous barbiturates became popular during World War II and is well reported on by Sargant and Slater (1940) More recently Rees Annear and Crosse (1950) have reported on the use of trichlorethylene narcosis claiming that it is safer and easier to use than either ether or intravenous barbiturates Most authorities are agreed that abreactive techniques are of greatest use in cases of acute traumatic neurosis such as occur during war or following train accidents Very frequently drug narcosis aids in producing a state of true disassociation and when this state is produced its effect is usually very much better Hypnosis without a narcotic drug is however frequently even more effective

Continued Narcosis The treatment of psychiatric patients by providing 16 to 24 hours sleep per day for periods up to about 10 to 14 days is gradually falling into disuse It has been recommended as a method of treatment in agitated melancholia some workers claiming that it removes the agitation but this is by no means always the case and the agitation disappears when the depression is relieved with electric convulsive therapy There is certainly no need to subject the patient to continued narcosis prior to giving electric convulsive therapy Continued narcosis still finds a place however in the treatment of the very acute anxiety state and can be used to tide a patient over the distress following an acute emotional shock The best drugs to use are somnifaine sodium amytal and paraldehyde Not more than about 40 ccs of somnifaine should be given in any one period of ten days When somnifaine is used no other barbiturate should be used to increase the degree of narcosis Full details of the technique can be found in standard works on physical methods of treatment in psychiatry

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ALCOHOLISM

The treatment of alcoholics is fraught with disappointment as any one who has treated such patients is aware They are a very serious challenge indeed and any method which offers hope is worth consideration

Conditioned Reflex Treatment The so called conditioned reflex treatment of alcoholism has been reported on fully by Voegtlin and

Many patients with a mild depression complain of early waking rather than any real difficulty in falling asleep and "Enseal" seconal ($1\frac{1}{2}$ to 3 grains) can be extremely useful for such patients as the full effect of the drug is present at the time when it is most required. For old people sedatives present a special problem. On the whole they respond very badly to opiates and frequently also to barbiturates. Both these groups of drugs tend to depress cardio-respiratory function and thus provoke cerebral anoxia. As cerebral anoxia is frequently responsible for the restlessness of the aged at night, it is preferable to use a sedative which stimulates cardio-respiratory function. Although despised and disliked by many physicians and most patients, paraldehyde is still perhaps the safest hypnotic for the restless elderly patient. Paraldehyde is best given as a draught by mouth with 2 drams of paraldehyde in two ounces of warm water flavoured with orange. As a guide to repeated dosage, approximately 1 dram per hour can be given for 24 hours. By intramuscular injection the maximum single dose is about 10 ccs, but 5 to 6 ccs is a more usual dose.

Amphetamine Sulphate. Amphetamine sulphate has quite definitely found a place in psychiatry and is undoubtedly helpful to many mild depressives. In doses of 5 to 10 mgms. on rising and at mid-day, it does help remove lethargy and lassitude. A more recent use of amphetamine has been its employment in acute barbiturate poisoning, and it does appear that given intravenously it may complement the effect of picrotoxin in promoting recovery from barbiturate coma (Nabarro 1950). The dosage of intravenous amphetamine recommended is in the region of 10 to 20 mgms. as an initial dose followed by about 20 mgms. every half hour in a glucose saline drip. The stimulating effect of amphetamine sulphate has led to a search for other drugs likely to have an euphoric effect. Synhexl (10 to 20 mgms. daily) which is a synthetic product resembling cannabis indica was favourably reported on by Stockings (1947). The work of Stockings, however, was not confirmed by Parker and Wrigley (1950) who state that although the drug has an undoubted euphoriant effect it fails to influence pathological depression. Rudolph (1949) has reported favourably on the effect of desoxyephedrine (methedrine) on depressive patients, but personal experience suggests that the claims made for it are too enthusiastic. The initial dose used is $2\frac{1}{2}$ mgms. before breakfast. The dose is increased slowly every few days until a total of 10 mgms. per dose is being given, and a total of 30 mgms. between rising and mid-day. Reaching such a dosage is a slow process and takes approximately 24 days.

Abreactive Techniques. The use of anæsthetics or intravenous barbiturates for producing emotional abreaction is by no means new. Ether was used to produce abreaction in 1917 by Starkey. The use

Broz (1949) Briefly the method of treatment is to give emetine hydrochloride at the same time as an alcoholic drink Patients can gradually be conditioned until the smell sight and taste of alcohol will produce severe nausea and vomiting It is even said that they can be conditioned to such a degree that the mere sight of a bar is sufficient to produce nausea This treatment requires special institutional care and cannot be done on an outpatient basis Analysing their case material which consists of 3 125 admissions over a period of 10½ years they state that 55 per cent remain abstainers for three years or more It is interesting to note that the prognosis is worse in lawyers, dentists and physicians !

Antabuse (Tetraethylthiuramdisulphide) First reported on by Hald and Jacobsen (1948) this drug is the result of a search for a substance which whilst being non toxic in itself, will produce toxic symptoms in combination with alcohol Antabuse itself is relatively non toxic in the normal dosage given Its only toxic effect in the usual dosage is a very mild sedative one but this is unnoticed by many patients The toxic symptoms produced with the ingestion of alcohol consist of flushing of the face which spreads down into the neck and upper chest tachycardia palpitation and a general feeling of oppression and distress These symptoms will follow the ingestion of one ounce of alcohol when the patient is under treatment with antabuse Further ingestion of alcohol results in nausea and vomiting in addition to the above symptoms and may ultimately lead to cardio vascular collapse Such collapse requires treatment with coramine and oxygen and carbon dioxide Deaths have been reported but are rare It has recently been suggested (Johnvartio 1950) that intravenous iron will remove the toxic symptoms Patients with advanced cardiovascular disease are probably serious risks and should be avoided The dose recommended by Jacobsen is an initial dose of 1 5 to 2 5 grams per day for three to four days followed by 0 5 to 1 gram per day as a maintenance dose Once the patient is on his maintenance dose he is given a test dose of alcohol to demonstrate what will happen if he drinks A physician should be present when the test dose is done in order to make quite sure that the patient shows no untoward sensitivity to the drug It is considered that the symptoms produced are those of acetaldehyde poisoning, because antabuse probably interferes with the metabolism of ethyl alcohol at the stage where acetaldehyde is reached in its breakdown Jacobsen (1950) has reviewed th[illegible] with antabuse of a large series of cases and he has undou[illegible] considerable success Personal experience ver[illegible] is not entirely without toxic [illegible] whilst receiving the [illegible] One patient who was so

olish as to drink whilst taking antabuse in its initial stages had a vere attack of vomiting lasting 24 hours and this provoked an tack of delirium tremens Other patients who drank whilst under eatment with antabuse developed signs of peripheral neuritis and ne patient developed a transient Bell s Palsy It will be noted that i only one of these cases was antabuse alone responsible for any ymptoms In the other cases it was a combination of antabuse plus lcohol

Treatment can be given on an outpatient basis providing someone n the home supervises the patient and makes sure that no alcohol is tal en If the patient is requested not to drink for 24 hours he can then be given 0 5 gram of antabuse in the evening preferably in the presence of the physician *If he has been drinking during the day* he will of course develop a toxic but not a severe reaction If he has kept his word the patient can be instructed to take 1 gram the next day in two doses followed by 1 gram on the two succeeding days With this dosage namely 0 5 gram the first day and 1 gram for the next three days followed by a maintenance dose of 0 5 gram per day no toxic symptoms have appeared

Antabuse is undoubtedly of great psychiatric help because it demands a measure of co operation from the patient So frequently the alcoholic proclaims his intention to cease drinking and to do all he can to stop the habit When presented with a drug which will produce toxic symptoms if he does drink his bluff is called and some patients refuse to co operate and admit quite openly that they choose to go on drinking On the other hand some patients co operate and it has been found that they then co operate with psychotherapy

The real problem in alcoholism is the patient s personality In some cases this can be modified considerably once the patient has stopped drinking for a reasonable length of time So long as the *patient remains alcohol sodden psychotherapy is apt to be useless* Once the patient is in a sane mind however he is able to co operate and progress can be made The personality aberrations responsible for alcoholism frequently go very deep and are then relatively unamenable to therapy and under these circumstances the patient may co operate for a while and then relapse Nevertheless antabuse must be regarded as a very great advance in the treatment of alcoholism

Alcoholics Anonymous Alcoholic patients are frequently gregarious individuals and are thus treatable in groups The best organisation of this kind is Alcoholics Anonymous This almost takes on the *form of a secret society* but many cured alcoholics are helped to remain well by giving help to other people who are in the same plight as they themselves once were

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VOEGTLIN W L and BROZ W R (1949) Conditioned reflex treatment of chronic alcoholism *Ann intern med* 30 580

DEMENTIA PARALYTICA

General paralysis of the insane was the first psychotic illness to show response to physical methods of treatment Malarial treatment followed later by the hypertherm has already held sway for nearly 30 years The use of penicillin in the treatment of syphilis raised the problem of whether pyrexial treatment was necessary in addition in the treatment of general paralysis It has been stated both by Dattner (1948) and Martin (1948) that penicillin alone is quite as effective as combined penicillin and pyrexial treatment The amount of penicillin must be at least 5 mega units but a more usual dosage has been 10 and sometimes as many as 20 mega units have been given In assessing the success of treatment Dattner (1948) relies entirely on the changes in the spinal fluid He believes that the Wassermann reaction and colloidal tests do not mirror activities of the syphilitic process He believes that when the cell count has become normal and there is a definite diminution in protein at least six months after treatment has been discontinued in the majority of cases the activity of the syphilitic inflammation has been permanently checked and there is no need for further therapy

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ELECTRIC CONVULSIVE THERAPY

Convulsive therapy was originally used in patients suffering from schizophrenia In some such patients it produced good results but later long term follow up has shown that they are not lasting Convulsive therapy was also tried in various depressive states and it is in these that it has proved beneficial It now has a definite place in psychiatric treatment amply justified by results

Kalinowsky (1948) in discussing failures with electric convulsive therapy (E C T) has classified the failures under three headings —

(i) Where the treatment was not indicated on clinical grounds
(ii) Where the treatment was indicated but was applied inadequately
(iii) Where treatment appeared indicated and was given adequately but still resulted in failure

It was originally felt that E C T would benefit all states of depression even those so called reactive or neurotic depressions which are usually related to environmental stress Kalinowsky like most psychiatrists believes that such conditions do not respond to electrical treatment and that the essential indication for this is a psychotic or endogenous depression This difference in therapeutic response renders the differential diagnosis between neurotic and psychotic depression a matter of great importance A few psychiatrists believe that there is no essential difference between the two conditions Mixed states certainly occur but at the extreme of the scale these illnesses are vastly different and the majority of experienced observers consider endogenous depression a fairly well defined clinical entity Certainly in the majority of cases an adequate clinical history will permit a diagnosis which is not only accurate from a nosological point of view but which is valuable in predicting the response to treatment

The symptoms of endogenous depression vary considerably Depression is always present in greater or lesser degree but may not be a spontaneous complaint Instead the patient may complain of difficulty in thinking and concentration and of general loss of interest both in work and amusements Some degree of agitation is frequently present and the patient complains of general nervousness and somatic symptoms such as palpitation and trembling In more severe cases hypochondriasis may be a marked feature and this may lead the patient to the general physician and to involved investigation for the hypochondriacal complaint Insomnia is an almost constant feature The main difficulty however is in not falling asleep but in waking at intervals during the night and particularly in the early hours of the morning The symptoms vary relatively little from day to day but in the majority of cases they are definitely worse in the morning and improve as the day wears on

Neurotic depressive symptoms on the other hand tend to vary considerably from day to day and to be worse later in the day These patients have difficulty chiefly in falling asleep rather than the type of insomnia seen in the depressive patient

Recurrent depression of the manic depressive type is extremely common and an average individual attack lasts from three to nine months Many such patients show no manic episodes Spontaneous remission is the rule The involutional type is slightly different Usually there has been no previous attack of depression and it is

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curare It must be admitted that the death rate from thiopentone anæsthesia and the death rate from curare are probably both larger than the death rate from E C T It is quite unnecessary to give so much curare that the muscular part of the fit is abolished and a very moderate dose will diminish the intensity of muscular movement sufficiently to avoid fractures and under these circumstances the use of thiopentone is probably unjustifiable Where the patient is extremely anxious prior to treatment sodium amytal 3 grains given at least half an hour before treatment is effective

The use of E C T as an outpatient method of treatment is debatable Mallinson (1948) has reported favourably on its extensive use in out patients The difficulties that arise with outpatient treatment are in the later stages when patients are apt to become somewhat confused and on occasions even mildly excited One must always warn relatives about such a possibility and one must always have a bed available in case of such an eventuality Outpatient treatment however has a place as by its means many patients can be persuaded to have treatment who would otherwise be untreated because of their refusal to enter hospital

Treatment of patients with E C T in the ordinary medical wards of the general hospital has however a very definite place Many mild depressives object quite strongly to going into a mental hospital and their relatives support them in this attitude They are however willing to come into an ordinary general hospital and can be quite adequately treated there

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ELECTRONARCOSIS

This method of treatment is really a modification of E C T The instrument used is so designed that it is capable of producing a steady current despite variation in the patient s head resistance A current of about 170–200 milliamperes is passed initially and this produces a tonic contraction After about half a minute the current is reduced to between 50–70 milliamperes until respiration starts again When this occurs the current is slowly increased to about 120 milliamperes the increase in current being at such a rate that a state of slight spasticity and unconsciousness is maintained If the current is increased too slowly the patient regains consciousness If it is increased too quickly the tonus becomes so severe that respiration may again be arrested The patient is maintained unconscious for a period of about seven minutes Treatment is given two to three times a week and as

fairly true to state that once recovered from an attack of involutional melancholia the patient does not tend to have further attacks Agitation is usually a very marked feature in involutional melancholia and the condition is frequently regarded as an anxiety state Hypochondriasis may be very marked and renders the prognosis worse Kalinowsky (1948) believes that therapeutic failures are extremely rare in recurrent depressions of the manic depressive group and that many of the failures particularly in the involutional group of melancholics, occur in the so called paranoid type These patients have generally inadequate personalities are complainers about others show hysterical features as an overlay to their depression and tend to be severely hypochondriacal He believes that this group are probably related to schizophrenia rather than to manic depressive psychosis

The number of electric convulsions required for the relief of depression varies between four and sixteen but the majority of patients require between six and ten treatments Personal experience shows that the treatment must be continued for some time after clinical recovery has been obtained Usually two or three treatments are required after the depression is relieved as an insurance against early recurrence Usually three treatments per week are quite frequent enough Given more frequently than this confusion is apt to become rather severe In older people it is sometimes advisable to give only two treatments weekly Where agitation is extremely severe frequent early treatment gives excellent results and even two treatments in one day may then be justifiable

Electric convulsive therapy also has a definite place in the treatment of mania In such patients treatment has to be given rather more frequently although the total number of treatments may not be greater than the number given to a depressed patient In the initial stages at least one shock daily is required and in some cases it is better to give two per day for about three days followed by one per day for another three days with one or two further treatments at more spaced intervals Such a course of treatment very frequently cuts short an attack of manic excitement During the treatment of mania with intensive E C T it is quite useful to tube feed the patient immediately following therapy When two shocks are given on the same day the second shock following immediately on the first a reasonably long period of post epileptic coma follows during which extensive nursing measures can be carried out

Further refinements have been attempted in the administration of E C T The use of curare or myanesin in order to diminish the severity of the tonic and clonic stages of the fits is now well established Owing to the distress that curare may produce in the patient many believe that it is better to use thiopentone anæsthesia before administering

curare It must be admitted that the death rate from thiopentone anæsthesia and the death rate from curare are probably both larger than the death rate from E C T It is quite unnecessary to give so much curare that the muscular part of the fit is abolished and a very moderate dose will diminish the intensity of muscular movement sufficiently to avoid fractures and under these circumstances the use of thiopentone is probably unjustifiable Where the patient is extremely anxious prior to treatment sodium amytal 3 grains given at least half an hour before treatment is effective

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many as 20 to 30 treatments may be given Paterson and Milligan (1947) have described the technique in detail and they have also reported favourable results in schizophrenia Garmany and Early (1948) have reported unfavourably on its effect in schizophrenia and they report "we find little evidence that electronarcosis has contributed to the physical therapy of the psychoses" Linford Rees (1949) has produced some figures showing results of treatment of schizophrenics with insulin electronarcosis and E C T compared with a control group From these figures it is seen that deep insulin treatment is the only method giving a significantly higher proportion of recoveries than the control group Monro (1950) has reported more favourably and suggests that electronarcosis is an equally safe alternative if insulin therapy is not available and he believes that electronarcosis has a useful place in the treatment of schizophrenia

On the whole electronarcosis has not been greeted with any degree of enthusiasm and the results so far obtained are somewhat open to doubt There is some evidence however that certain schizophrenic patients who have not responded to insulin coma therapy may respond to electronarcosis

Electronarcosis has an effect on the affective disorders similar to that of E C T As the intensity of the tonic stage is not so severe as in E C T it is occasionally used as a substitute where there is a danger of physical injury to the patient It is doubtful if this is any better than using E C T with curare which on the whole is somewhat simpler

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INSULIN COMA THERAPY

Insulin coma therapy was introduced by Sakel in 1933 and by 1938 was being used in most of the civilised countries of the world It is now used in the treatment of schizophrenia in almost every mental hospital in this country

The actual technique of treatment is well described by Kalinowsky and Hoch (1946) and Sargant and Slater (1948) and details will not be given in this chapter An enormous amount of statistical work has now been done on the value of insulin coma therapy It will have been noted that in discussing electronarcosis insulin coma therapy appeared to be the most satisfactory treatment of schizophrenia Originally E C T was used for schizophrenia and there is no doubt that it is capable of producing temporary remissions A long term

follow up however of schizophrenic patients treated with E C T shows that the initial improvement is not maintained and that the end result in an E C T treated group is no b tter than that of a control group Insulin coma therapy on the contrary can be shown to increase the percentage of permanent remissions A Temporary Commission on State Hospital problems in New York in 1944 produced a series of figures based on a very large number of cases Their figures include 1 128 schizophrenic patients treated with insulin and a control group of 897 schizophrenic patients who received no physical treatment Of patients treated within the first year of their illness 80 per cent left mental hospital In the control group the comparable figures is 59 per cent Analysis of the cases under clinical headings reveals —

In the paranoid group the remission rate rises from 52 per cent to 79 per cent with insulin treatment

In the catatonic group from 65 per cent to 81 per cent

In the hebephrenic group from 59 per cent to 68 per cent

The relapse rate among all cases was 42 per cent in the insulin treated group and 31 per cent in the untreated group The Commission said that when patients are treated with insulin their average stay in hospital is reduced by four months and that the quality of the remission obtained is better than that which occurs spontaneously They also state that the treatment has little effect on patients who have been ill for more than two years Freudenberg (1947) reports favourably on the use of insulin coma therapy in schizophrenia but points out that certain symptoms worsen the prognosis So called process symptoms e g schizophrenic thought disorder hallucinations primary delusions and passivity feelings are all unfavourable He points out that the more atypical the schizophrenia the better the prognosis and the more closely does schizophrenia resemble an affective disorder the better the prognosis

Untreated schizophrenia has an extremely poor prognosis and probably about 70 per cent of such patients ultimately end their days in a mental hospital The prognosis when the patient has been ill for one year is very poor and after two years as already quoted treatment has little effect It is thus very important that early diagnosis of schizophrenia should also lead to early treatment, and it is quite wrong to leave untreated a mild early case merely because the patient is managing to show some degree of adaptation to society One of the reasons that the catatonic cases do so well is that the onset of the disorder is apt to be acute and florid—often so florid that there is no option but to admit the patient to a mental hospital Hebephrenic patients on the other hand are apt to have a very slow and insidious onset and frequently do not arrive in the physician s consulting room until they have been ill for a very long time In fact it is

often very difficult to decide how long the patient really has been ill and one occasionally sees patients in the early twenties who show some evidence of personality deterioration extending over a period of several years In these cases little is to be gained by early admission to a mental hospital and it is much better to do what one can to assist the patient to adapt to society even if he has to be accepted as an invalid Owing to the serious overall prognosis of the disorder it is probably justifiable to give insulin treatment when one is in doubt as to its value The number of lasting remissions obtained in such circumstances may be very small indeed, but the occasional success makes the treatment worth while

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PRE FRONTAL LEUCOTOMY

Coincidental with the development of the so called shock therapies Moniz (1936) was experimenting on a surgical approach to the treatment of psychotic illness His technique became refined and has now become well known under the name of pre frontal leucotomy The surgical details of the treatment and review of results obtained are well covered by Freeman and Watts (1942) It is interesting to note that there was a long gap between Moniz describing his treatment and the treatment being developed and coming into general use It was first used in this country in 1941 and the first report of any considerable number of patients treated by this method was given by Meyer Beck and McLardy (1947) A more recent review of a large series of cases treated in this country is that of Partridge (1950)

Shock treatments did and still do cause a good deal of emotional opposition partly because the treatments are felt to be crude and also because of their empirical nature Leucotomy is again empirical, and it does produce its own untoward results which cannot of course be undone In view of this great caution is required before recommending such a drastic irrevocable step Nevertheless drastic and irrevocable steps are frequently taken in medicine and sometimes a condition is so distressing that no treatment which offers hope of relief can be rejected This is true of leucotomy, as there is no doubt that many chronic psychotic patients have been greatly relieved by its aid, and in our present state of medical knowledge there is no

other treatment available which would produce this result Leucotomy is a crude operation and its results are apt to be uncertain The fact that it does produce relief has stimulated a great deal of research and out of this will no doubt be developed more exact methods of treatment

Briefly leucotomy is of benefit in patients showing —

(i) Chronic tension such as is frequently seen in obsessional states

Obsessional states probably cover a multitude of illnesses and many of them are undoubtedly psychotic in mechanism and are not simply neurotic manifestations It is in the patient with a severe obsessional state as a result of an underlying psychosis that the best results are obtained Where the obsessional state shows a considerable amount of variability as it frequently does in neurotics it is doubtful if such a drastic step is justifiable

(ii) Chronic states of depression particularly with agitation

Chronic depressive states frequently arise in middle age and sometimes later Many of these of course respond to E C T and this is obviously the first treatment of choice Where such treatment fails and the patient continually relapses leucotomy should be considered It is interesting that there is some evidence that when a patient benefits from convulsive therapy and then relapses the prognosis with leucotomy is likely to be quite good The atypical depressive with marked hypochondriasis may or may not benefit depending upon whether or not the hypochondriasis is secondary to the depression in mood When secondary to depression of mood benefit is likely but when hypochondriasis takes on the nature of a primary delusion and is not secondary to a change in mood little benefit is likely to accrue and many failures have occurred in such hypochondriacal patients

(iii) Many schizophrenic patients have been subjected to leucotomy and many of the results have been disappointing If there is a great deal of emotional tension as a major factor in the patient s symptoms benefit is likely but apathy thought disorder and primary delusions are unlikely to be affected Leucotomy in itself tends to produce apathy lack of social tact and general lack of foresight Certain paranoid schizophrenics have very marked emotional tension in their hallucinosis and delusions It is obvious in such cases that the emotional tension is a driving force for their symptoms and leucotomy may relieve them The drive behind their delusions is diminished but their content remains The patient however is given some degree of freedom from

preoccupation with delusional material and is thus able to take an interest in other things With encouragement such a patient can be rehabilitated and may make a social recovery

In deciding on leucotomy, diagnosis as such is of little importance The constellation of symptoms present, however is much more important An understanding of the effects of leucotomy both good and bad, will enable one to make some forecast of the post operative state in a particular patient One can decide that tension and depression of mood may diminish and that symptoms secondary to such tension and changes in mood will also diminish One will however, introduce a general indifference lack of tact and social discrimination and general lack of foresight If the patient has been an over scrupulous rather shy, retiring individual a diminution in social tact may not be noticeable and may even be to the patient's advantage! On the other hand if the patient was a rather intolerable social boor completely lacking in tact and foresight, such faults of personality are likely to be made worse and the patient may be socially intolerable after leucotomy It must be stressed again that the decision to advise leucotomy is a serious one Nevertheless to avoid ever recommending it lest one makes a mistake is merely a convenient way of escaping clinical responsibility

Many patients and their relatives, and for that matter many physicians feel that leucotomy will be followed by intellectual changes The evidence however is against this (Freudenberg 1949) and the intellectual performance of a patient after leucotomy is frequently better than when he was ill and not demonstrably worse than when he was well

The mortality rate from pre frontal leucotomy is quite low and in skilled hands is in the neighbourhood of two per cent There are certainly elderly patients who will tolerate leucotomy better than convulsive therapy, and in chronic depression in the elderly it is sometimes an extremely effective step

Meyer and McLardy (1948) and McLardy (1950) have reported upon uræmic and trophic changes following leucotomy These changes have sometimes resulted in the death of the patient Death may occur from such causes about two to five months after operation The post mortem findings suggest that damage to the premotor regions the putamen the caudate nucleus the posterior parts of the orbital regions and in structures lying between these is responsible These patients tend to become marasmic with multiple cutaneous septic sores within two to five months after the operation the whole condition being termed for the want of a better name trophic deterioration'

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TOPECTOMY

Following upon the partial success of leucotomy attempts have been made to refine the operation and to confine the damage done to the frontal lobes to the bare minimum necessary to produce beneficial results and to avoid if possible some of the ill effects produced by leucotomy in the spheres of emotion and behaviour Anatomical evidence has shown that the region of the medial nucleus of the thalamus which most frequently shows retrograde change in the human being after leucotomy is that which projects to Area 9 of the cortex—the term Area 9 applying to Brodmann s areas of the cortex It has been suggested that functional changes due to dis connection of Area 9 might be the critical factor in leucotomy regardless of whatever other changes might result from disconnection of additional areas Localised cortical ablation of certain areas has been named topectomy The areas largely removed by operation are Areas 9 and 10 of Brodmann the operation being a bilateral one The general conclusions with regard to such operations are that patients are much less anxious after operation and have not the marked change in personality which usually follows leucotomy Re search continues into which areas and how much of them should be removed to produce the desired result An excellent description of the treatment of 48 patients by topectomy is Selective Partial Ablation of the Frontal Cortex edited by Mettler This is a detailed survey which covers the anatomy physiology psychology surgery and results of the operative procedure It already appears that topectomy may well become the operation of choice rather than the somewhat crude operation of pre frontal leucotomy

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CHAPTER XIII

THE CHRONIC RHEUMATIC JOINT DISEASES

by

PHILIP ELLMAN

Ætiology Classification Pathology Treatment (Cortisone and A C T H) Rheumatoid heart disease Rheumatoid lung disease Clinical manifestations of the rheumatoid type of arthritis Atypical forms of rheumatoid disease Psychosomatic aspects of chronic non articular rheumatism Gout

ÆTIOLOGY

THE chronic rheumatic diseases comprehend many medical diseases of the musculo skeletal system but as we hope to show it is in fact a mesenchymal disease Regarding its exact ætiology our knowledge has regrettably not advanced and remains to day in the position of tuberculosis in 1882 before Koch had discovered the tubercle bacillus Of the many ætiological factors that have from time to time been incriminated in relation to the rheumatoid type of disease focal sepsis has in the past held pride of place As a result it has been a common occurrence to find patients divested of teeth and tonsils perhaps with sinuses drained or gall bladder appendix and other organs removed Yet in spite of such radical measures the patient is seldom any better —on the contrary he becomes despondent and lowered in morale The specialised surgeon whether oral surgeon gynæcologist or urologist may, in all sincerity report some deviation from the normal in cases of arthritis of the rheumatoid type but Vaizey and Clark Kennedy (1939) among many others have supplied an admirable corrective in relation to chronic rheumatism and they point out that the cure of

the rheumatoid type of arthritis following dental extraction is the exception rather than the rule and that bad teeth are not incompatible with good general health Experience would suggest that in some two per cent of cases of so called secondary focal infective arthritis removal of a carefully assessed focus of sepsis may produce a dramatic response

The possibility of a virus as the cause of rheumatic fever was first postulated by Schlesinger and his colleagues in 1935 The concept was upheld by Eagles Timbrell Fisher and others (1937) and extended to rheumatoid arthritis and has been confirmed by Sabin (1939) at the Rockefeller Institute in experimental animals

The theory of bacterial allergy conceives the acute and chronic rheumatisms as anaphylactic diseases with multiple lesions in the mesodermal system produced by continual antigen antibody reactions in or on tissue cells Visceral and other lesions might be explained as hypersensitivity manifestations in tissues elsewhere in the body

Rheumatoid Disease whose principal clinical manifestation we believe to be arthritis is now generally accepted as a systemic disease with local manifestations sometimes widespread and not necessarily confined to the locomotor system In the writer s view the clinical picture should be conceived in wider terms and exclusive concentration on the joint lesions may well be an explanation of our present ignorance in relation to ætiology For example in rheumatoid disease extra articular changes, apart from the inflammatory joint lesions may be observed in tendons bursæ skin and subcutaneous nodules peripheral nerves muscles the eye and as we shall indicate later in the heart lungs pleura kidney spleen lymph glands and other organs

Levinthal (1943) believes that the debility of the antibody producing system—the reticulo endothelial system—is the basic cause of rheuma tism and that all other indirect or precipitating factors interfere with the function of antibody production or maintainance of the state of perfect immunity The concept is attractive appears rational and lends support to the unitary theory it offers some integration of the rheumatic group of diseases and suggests a relationship between the acute rheumatoid type of arthritis and rheumatic fever It would account too for the incidence of eight per cent of cases of rheumatic carditis in 100 consecutive cases of rheumatoid arthritis in the writer s series The traditional concept of a pure bacterial infectious ætiology in all cases of the rheumatoid type of arthritis must be resisted if we are to make any real progress Certainly if there were anything in the hæmolytic streptococcal theory there should have been a thera peutic response to sulphonamide or penicillin therapy

The anaphylactic hypersensitivity basis of both rheumatic carditis and arthritis is suggested by Rich and Gregory (1943) to denote a

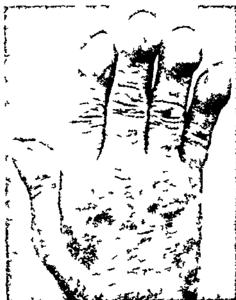



Fig 35



Fig 36

FIG 35 Photograph of the hands of a male aged 61 with pulmonary osteoarthropathy and rheumatoid polyarthritis involving the metacarpo phalangeal joints of the wrist the knee and ankle Apart from the soft tissue swelling involving the fingers toes and nose there was periostitis of the long bones and joint swellings with effusions into both knees

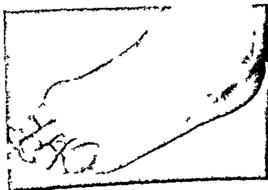


Fig 36 Feet and ankles of the same patient The patient had a bronchial carcinoma involving the right upper lobe (Fig 37) A lung resection was performed by Mr R C Brock and within 48 hours of the operation the patient who was grossly disabled through his polyarthritis had a marked reduction of joint swellings and a full range of movement of all his joints The result was dramatic

variable tissue response to the same noxious agent The question then arises as to whether such conditions as the Still and Felty syndromes spondylitis ankylopoietica psoriasis arthropathica and Reiter s



Fig 3 Legend on opposite page

syndrome of non specific arthritis urethritis and conjunctivitis well described by Vallee (1946) can be similarly explained as hypersensitivity manifestations Rich has indicated an even wider association on the basis of hypersensitivity between rheumatic fever the rheumatoid type of arthritis and such obscure conditions as acute disseminated lupus erythematosus polyarteritis nodosa dermatomyositis and scleroderma for there is no doubt that certain clinical and pathological manifestations are shared Furthermore anatomical studies have shown alterations of some constituents of connective tissue consisting in the main of collagen fibrils and interfibrillary substance or cement The last named contains complex polysaccharides such as hyaluronic acid and an enzyme hyaluronidase which when it attacks hyaluronic acid and other ground substances of connective tissue can produce changes analogous to those seen in rheumatic disease although up to the present no direct association between hyaluronic acid metabolism and rheumatism has been established (Cohen 1949)

These mesenchymal connective tissue diseases have been grouped under the collective title of collagen diseases or systemic collagenoses

Collagen is found in skeletal tissues such as connective tissue fascia muscle, ligament joint capsule synovial membrane articular cartilage and bone and may also be present in blood vessels supplying these and other tissues The vascular changes are those of an arteritis which may involve all coats of the vessels as part of a fibrinoid necrosis of collagen, giving rise to so called rheumatoid granulomata '

In certain cases an association between chronic rheumatic joint disease and endocrinal dysfunction appears evident Selye *et al* (1944) produced experimentally in adrenalectomised animals a polyarthritis resembling histologically that seen in rheumatic fever and even in rheumatoid arthritis following over dosage with desoxycorticosterone acetate thereby demonstrating the possible role of the adrenal glands Urbach (1944) has suggested that this may be an allergic reaction the pathological lesions being the clinical expression of an allergy to the adrenal cortex It must be noted however that extensive investigations have not revealed any significant abnormality in the endocrine system in rheumatoid disease

The potential significance of the pituitary in relation to chronic rheumatism notably in women has received considerable attention and X ray irradiation of the pituitary has been postulated as a possible line of treatment while Fried (1943) has suggested that the connection between acromegaly and pulmonary osteoarthropathy may well be due to a dyspituitarism akin to acromegaly Typical rheumatoid joint lesions with pulmonary osteo arthropathy have been found in four cases under our care to be associated with intrathoracic tumours (Ellman 1947) (bronchial carcinoma in three cases) Removal of these tumours has shown a dramatic improvement in the joint condition within 48 hours (Figs 35 36 and 37) Holmes *et al* (1950) have reported seven patients in whom pulmonary osteoarthropathy was associated with pulmonary neoplasia and in whom surgical removal of the tumour relieved the joint symptoms Finally the exacerbation of rheumatic symptoms before the menses and remission during pregnancy have been noted as yet other possible contributory endocrinal factors

Extraneous factors can be held to some extent responsible for the development of chronic rheumatic disease—damp and cold probably being less important than dirt excessively heated and ill ventilated houses and overcrowding Lack of a protective diet may also be an accessory to the development of the disease although no specific diet is known for its treatment

In an investigation into the ætiology of rheumatoid arthritis (1950) by the Scientific Advisory Committee of the Empire Rheumatism Council 532 patients with the rheumatoid type of arthritis and 532 controls comparable in age sex and civil state were investigated in

relation to the significance of various factors widely alleged to be ætiologically significant These factors included sex incidence and age of onset psychological precipitating factors the presence of focal sepsis familial incidence of arthritis the effect of previous pregnancies and parturition home conditions occupation the relation of weather and season and of abnormalities of the peripheral circulation

An interesting feature that emerged was that the alleged ætiological factors produced largely negative results and many were found to occur as often in controls as in patients Accordingly the danger of accepting uncontrolled clinical impressions without critical statistical analysis in this as in other diseases must be borne in mind On the other hand, such factors as the familial incidence of the disease the adverse influences of cold and damp and the presence and significance of abnormalities of the peripheral circulation ante dating the onset appeared to warrant further investigation

Recent work of Selye (1950) on the General Adaptation Syndrome (G A S) suggests that rheumatoid disease may belong to a group of diseases which develop as a result of failure of the body to adapt itself to prolonged stresses and strains If this hypothesis is accepted it is possible but not proved that certain physical psychological and infective states might produce rheumatoid disease in persons with an abnormally weak adaptation mechanism

The favourable effects of a hormone of the adrenal cortex (17 hydroxy 11 dehydrocorticosterone Compound E) and of pituitary adrenocorticotrophic hormone (A C T H) in inducing the potential reversibility of rheumatoid arthritis raises the possibility that we may in fact be dealing with a basic biochemical disturbance but there is as yet no true evidence to indicate that rheumatoid disease and adrenal cortical insufficiency can be correlated

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(a) Classical type of rheumatoid arthritis of women usually of child bearing period

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B Osteoarthritic type (hypertrophic degenerative)

(a) Known ætiology

(1) Secondary to trauma

(2) Secondary to arthritis of rheumatoid type

(3) Associated with disordered metabolism (climacteric gout scurvy hæmophilia)

(4) Associated with organic disease of the nervous system (e g Charcot s joints and syringo myelia)

(b) Unknown ætiology

So-called senile variety (e g morbus coxis senilis)

Group 3 Non articular affections

PATHOLOGY

We propose to concentrate on the type of rheumatoid disease in which pathological investigations have shown some significant progress

The pleomorphic histological features are well known As far as the joints are concerned the synovial membrane is first involved and following the inflammatory process becomes congested œdematous, thickened and hypertrophied being ultimately converted into a highly vascular structure of granulation tissue At this stage varying degrees of effusion occur in the form of inflammatory exudates the total cellular content of which varies according to the acuity of the disease from a few thousand to as much as 50 000 or 60 000 per c mm with a preponderance of polymorphs sometimes reaching 90 per cent The fluid is sometimes clear frequently turbid and never truly purulent In more severe cases there is increased clot formation decreased viscosity an average protein content (derived from the blood plasma) of about 4–5 gm and a reduced fasting sugar content Culture of the fluid is sterile Histologically the synovial membrane shows focal collections of lymphocytes with a characteristic structure of a central zone of large epithelioid cells surrounded by a dense collection of small round celled (lymphocytic) infiltrations which may but not necessarily be perivascular As the disease progresses a pannus of this highly vascular hypertrophied granulation tissue spreads over the joint cartilage producing erosion and destruction

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- (4) Arthritis following other specific infections such as dysentery scarlet fever rheumatic fever

(*b*) Non specific causation Unknown ætiology
- (1) With known associated factors
  - (*a*) Metastatic or focal arthritis including the so called multiple infective arthritis
  - (*b*) Associated with disordered metabolism (e g, gout)
  - (*c*) Climacteric arthritis (Villous type)

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nodules of acute cases have much in common with rheumatic fever The chronic nodules have been aptly described by Parkes Weber and others as necrobiotic nodules Dawson (1935) in comparative studies of subcutaneous nodules in rheumatic fever and rheumatoid arthritis believed them to indicate the close relationship of the two diseases and that they were possibly different responses of affected individuals to the same ætiological agent Raven Weber and Price (1948) describe a case of a grossly deformed arthritic subject who at autopsy had an extensive distribution of necrobiotic nodules They were found on the scalp and the elbows, in the larynx and the muscles, and in the internal organs including the lungs pleuræ, pericardium and heart muscle In addition to the advanced arthritic changes there were pericarditis endocarditis mediastinitis, bilateral pleural effusions and perisplenitis The case suggested to the authors that the disease should perhaps be classified with the infective granulomata together with tuberculosis syphilis and leprosy They also noted its relationship to acute disseminated lupus Bennet Zeller and Bauer (1940) have described a similar case with widespread necrobiotic nodules and pericardial and pleural involvement.

Focal lesions in *peripheral nerves and muscles* as a part of rheumatoid disease have been described by Freund and co-workers (1942 1945) and Kellgren and Ball (1950) have studied in detail earlier Scandinavian work on the tendons as a site of rheumatoid disease We shall have occasion later in a consideration of the variants of rheumatoid disease and some of its visceral manifestations to refer to the conditions of rheumatoid heart disease and rheumatoid lung disease

It is not surprising that in a disease of such chronicity cases exhibiting *amyloid disease* have been discovered

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TREATMENT OF RHEUMATOID DISEASE

In spite of the striking results of Cortisone and A C.T H therapy reported by Hench and his co-workers we feel that Hench himself would be the first to utter a warning against relaxation of the basic principles of treatment The need for maintenance to avoid relapse

A similar inflammatory change affects the endosteum of the epiphyseal bone marrow which is thus destroyed from above and below Since the ends of the two articulating bones are destroyed and bridged over by granulation tissue fibrous or even bony ankylosis may result, and this is generally associated with wasting of the neighbouring muscles In advanced cases the joint may be completely destroyed and the adjacent bone may become fused with a common bone marrow The result is in many cases a secondary bony osteo porosis with cystic changes and erosions well seen radiologically It should be mentioned that the synovial pannus may, and frequently does extend into the periarticular tissues, producing the characteristic spindle shaped deformity of the fingers

Among the *extra articular lesions* cutaneous but more commonly subcutaneous nodules are to be found on bony prominences especially the olecranon, subjected to pressure and trauma and in our experience they occur in some 10 to 20 per cent of cases (Fig 38)



Fig 38 Cutaneous and subcutaneous nodules in a case of acute rheumatoid polyarthritis The pathology of these nodules closely resembles that seen in rheumatic fever and is to be distinguished from the chronic necrobiotic nodules

The histological pattern is distinctive with a central zone of fibrinoid degeneration and necrosis surrounded by a radially arranged palisade layer of connective tissue cells At the periphery there is an area of dense fibrous avascular collagenous tissue constituting most of the nodule and made up of an agglomeration of smaller nodules The necrotic centre with fibrosis around the chronic nodules is characteristic of rheumatoid disease but certain of the more transient small

Manipulation and surgery of arthritic joints should only be advised in quiescent disease and it is the physician s responsibility to decide at what juncture to institute such measures and to weigh the indications or otherwise for joint aspiration arthrotomy partial synovectomy capsulectomy arthrodesis arthroplasty etc.

Diet There is no specific diet for the treatment of any of the chronic rheumatic diseases except in so far as the diet must be a protective one

Drugs The use of iron by mouth or intravenously to correct iron deficiency anaemia and gold therapy in active rheumatoid arthritis are now well known Vitamin therapy and insulin for malnutrition may also be valuable adjuncts to treatment Other drugs have been fully noted in a previous edition

After Care Must be adequate and sufficiently prolonged to avoid relapse

CORTISONE AND A C T H *

History of Discovery and Development *Cortisone* In 1936 Kendall and his co-workers isolated a steroid from the adrenal cortex later to be known as Compound E In the same year the identical substance was isolated by Wintersteiner and Pfiffner as Compound F and by Reichstein as Compound Fa

Compound E was shown by Mason Hoehn and Kendall in 1938 to be 17 hydroxy 11 dehydrocorticosterone In 1949 Compound E was renamed Cortisone Eight years after the elucidation of its chemical formula L H Sarett with Kendall and his co-workers succeeded in partial synthesis of Cortisone from desoxycholic acid

The first reported use of Cortisone in rheumatoid arthritis came from Hench Kendall Slocumb and Polley at The Mayo Clinic in April 1949 Since then numerous reports confirming their findings have appeared in the literature

A C T H In 1930 it was shown that removal of the anterior pituitary gland in rats resulted in adrenal cortical atrophy and that this atrophy could be prevented or corrected by daily transplants of anterior pituitary substance Collop in 1933 isolated an impure adrenotropic substance containing adrenocorticotrophic principle in potent amounts The pure form was obtained in 1943 by Li and collaborators from sheep pituitaries and by Sayers and co workers from pig pituitaries A C T H was first used therapeutically in myasthenia gravis by Soffer in 1948 and by Cohn in gout in 1948 It remained for Hench and his co workers in May 1949 to establish the use of A C T H on rheumatoid arthritis with results that are now well confirmed

* I am indebted to Dr John Murray for his help with this section

demands on adequate supply and we would agree that short interrupted courses are on the whole, less satisfactory than prolonged uninterrupted therapy (Boland 1951 Margolis and Caplan 1951) In the present state of our knowledge hormone treatment should be regarded as palliative In exactly the same way in the allied disease pulmonary tuberculosis, the newer antibiotics must be used as important ancillary aids, over and above the fundamental and basic sanatorium regime

Successful results still necessitate (*a*) the co operation of the patient which involves a frank explanation of the nature of the treatment involved, (*b*) a carefully planned regime particularly where the disease is active with considerable systemic disturbance as well as local involvement of many joints We are convinced that bed rest preferably in hospital to begin with, where all treatment facilities are available is imperative

Bed rest involving mental as well as physical rest must take into consideration body mechanics and a good position must be ensured to prevent deformity The mattress must be firm or have fracture boards beneath There must be a firm backrest reinforced by a single firm pillow and a knee cage should be used to prevent pressure from the bed clothes producing a foot drop "Kind" friends or nurses should in no circumstances be allowed to comfort the patient with knee pillows for the tragedy of ankylosed knees with resultant flexion deformities may ensue For *at least* one hour in the morning and one hour in the afternoon patients are encouraged to lie flat with one head pillow and if there is any shoulder involvement they should keep both arms behind the head to promote the movements of abduction and external rotation *Physical treatment* given by a competent physiotherapist, according to the detailed instructions of the physician usually involves varied forms of heat massage and re educational exercises which the patient is encouraged to learn as soon as possible *in order to become self supporting*

Orthopædic measures for the prevention and treatment of deformity The physician s concern is the prevention of deformity He must therefore, be familiar with the principles of orthopædic medicine in order to preserve and restore the function of involved joints The use of manipulation splintage and serial plasters dependent upon the general and local condition of the patient should be decided upon by joint collaboration between the physician and orthopædic surgeon The use of plaster of Paris splints for immobilisation of acute joints in the optimum position of ankylosis is an invaluable therapeutic measure For knee and ankle joints that are acutely inflamed it is an advantage to keep them in splints for three weeks before movements are begun In this way pain and swelling are reduced

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After Care Must be adequate and sufficiently prolonged to avoid relapse

CORTISONE AND A C T H *

History of Discovery and Development *Cortisone* In 1936 Kendall and his co workers isolated a steroid from the adrenal cortex later to be known as Compound E In the same year the identical substance was isolated by Wintersteiner and Pfiffner as Compound F and by Reichstein as Compound Fa

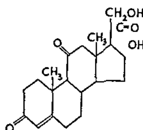
Compound E was shown by Mason Hoehn and Kendall in 1938 to be 17 hydroxy 11 dehydrocorticosterone In 1949 Compound E was renamed Cortisone Eight years after the elucidation of its chemical formula L H Sarett with Kendall and his co workers succeeded in partial synthesis of Cortisone from desoxycholic acid

The first reported use of Cortisone in rheumatoid arthritis came from Hench Kendall Slocumb and Polley at The Mayo Clinic in April 1949 Since then numerous reports confirming their findings have appeared in the literature

A C T H In 1930 it was shown that removal of the anterior pituitary gland in rats resulted in adrenal cortical atrophy and that this atrophy could be prevented or corrected by daily transplants of anterior pituitary substance Collop in 1933 isolated an impure adrenotropic substance containing adrenocorticotrophic principle in potent amounts The pure form was obtained in 1943 by Li and collaborators from sheep pituitaries and by Sayers and co workers from pig pituitaries A C T H was first used therapeutically in myasthenia gravis by Soffer in 1948 and by Cohn in gout in 1948 It remained for Hench and his co workers in May 1949 to establish the use of A C T H on rheumatoid arthritis with results that are now well confirmed

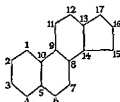
* I am indebted to Dr John Murray for his help with this section

Chemistry *Cortisone* Cortisone acetate is a nearly white powder soluble in water to 2 mgms per 100 cc Its formula is 17 hydroxy 11 dehydrocorticosterone



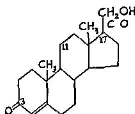
(a gluco corticoid)

The following is the manner in which the carbon atoms are numbered on the basic steroid formula —



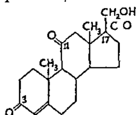
(the cyclo penteno phenanthrene system)

(1) It has been found that an unsaturated O at C3 and an alpha ketol group CH_2 OH = CO at C 17 are essential for mineral activity Thus desoxycorticosterone acetate (D O C A) possesses the formula —

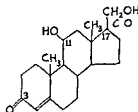


(a mineralo corticoid)

(2) The addition of an O at C11 leads to the formation of dehydro corticosterone (or Compound A) or of an OH at C11 to corticosterone (Compound B) thus —



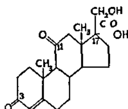
11 Dehydrocorticosterone
Compound A



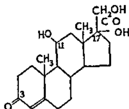
Cortico terone
Compound B

This addition reduces the mineral actuity and increases the action on carbohydrate metabolism

(3) Finally the addition of an OH at C17 to 11 dehydrocorticosterone leads to Cortisone and to Compound F if added to corticosterone further decreasing mineral activity and increasing the action on carbohydrate metabolism



17-hydroxy 11-dehydrocorticosterone
(Cortisone or Compound E)
(a gluco-corticoid)



17-hydroxy corticosterone
(Compound F)
(a gluco-corticoid)

ACTH The adrenocorticotrophic extract isolated by Li and co workers in 1943 was a protein very similar to that independently obtained by Sayers *et al* the molecular weight being 20 000

There is now evidence that the active principle may be of smaller molecular size as Li *et al* reported that 60 per cent of the protein could be digested with pepsin without loss of biological action

Action of Cortisone and A C T H

1 **Manner of Action** Injection of A C T H induces depletion of adrenal ascorbic acid and cholesterol and this process is accompanied by deposition of glycogen in the liver

All known types of adreno cortical hormones can be produced by the cortex under the action of A C T H and the overall effects of the hormones appear to depend upon their ratio

This mechanism is self regulating—Cortisone inhibits A C T H production It has been shown that stress elicits increased production of A C T H and that this effect can be inhibited by the corticoids The gluco corticoids are more effective in this inhibition than the mineralo corticoids

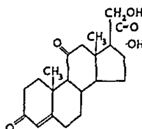
In summary the general physiological effects of Cortisone and A C T H are —

(1) Inhibition of protein synthesis—A C T H inhibits the action of the growth hormone which regulates the rate of protein synthesis This leads to increased blood amino acids and increased excretion of nitrogen

(2) Increased rate of gluconeogenesis —Gluco corticoids facilitate the synthesis of carbohydrates from fats and amino acids and increase the storage of glycogen in the liver

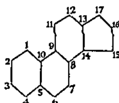
(3) Involution of the thymus and lymph nodes

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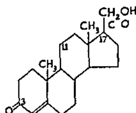
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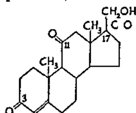
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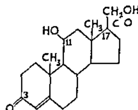


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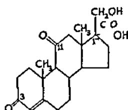
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Compound A



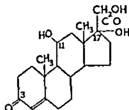
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(3) Involution of the thymus and lymph nodes

(4) Changes in electrolyte balance—namely, retention of sodium and chloride with increased excretion of potassium calcium and phosphates The latter changes may be associated with decreased chondrogenesis and osteogenesis with a reduction in plasma alkaline phosphatase

2 **Metabolic Effects** (1) *Plasma electrolytes* Average doses of Cortisone and A C T H induce minimal changes in the balance of nitrogen calcium, phosphorus sodium, potassium and chloride Larger doses induce negative balances for nitrogen, potassium, calcium and phosphorus with retention of sodium, chloride and water

(2) *Urinary Nitrogen Excretion* Small doses cause slight or no increase in nitrogen excretion while bigger doses cause a pronounced excretion

(3) *Carbohydrate Tolerance* Slight inconstant increases in fasting blood sugar levels have been observed in some cases

(4) *Corticosteroid Excretion* Urinary excretion increases initially with Cortisone and may remain elevated or drop to normal with increased or continued doses A C T H promotes increased excretion—30–50 per cent of the total amount excreted is Compound F indicating that A C T H stimulates the adrenal cortex to produce Compound F rather than Compound E

(5) 17 *Ketosteroids* Cortisone causes a prompt fall in urinary output of 17 Ketosteroids while A C T H causes a prompt increase

(6) *Serum Uric Acid* Significant reductions only occur when the initial level is high or high normal

(7) *Creatinine and Creatine* Increased creatinuria is only found constantly in the early phase of administration

(8) *Serum Protein* Serum albumin is increased and serum globulin reduced only if their pre treatment values are respectively low or high

3 **Physiological Effects** (1) *Hæmatopoietic* A C T H, and to a lesser degree, Cortisone cause a depression of circulating eosinophils, and lymphocytes with an increase in polymorphonuclears Red cells hæmoglobin reticulocytes and platelets tend to rise only if initially low

(2) *Cardiovascular* Hypertension may occur but is uncommon It is transitory during the phase of electrolyte and water retention

(3) *Psychological* Temporary euphoria feeling of well being depression restlessness insomnia nervousness mania and changes in the E E G patterns may occur

(4) *Collagen* Inflammation and fibroblastic proliferation tend to be inhibited with reduction in fever and pain of any cause

(5) *Immunity* Cells appear to be rendered more immune to a variety of toxic agents such as bacteria antigens and chemicals

Side Effects of Cortisone and A C T H (1) *Œdema* Can be minimised by a low sodium diet and high potassium intake

(2) *Weight loss* May be corrected by a high protein diet or administration of 25 mgms of Testosterone daily

(3) *Hyperglycæmia and Glycosuria* This is infrequent even on high dosage It may be controlled by reducing the dose or giving insulin

(4) *Hypertension* Rare—controlled by reduction of dose

(5) *Muscle weakness* fatigue exhaustion and paræsthesiæ These symptoms may be due to a potassium deficiency which may be seen in E C G as a lowering of the T wave or a depression of the S T segment This can be corrected by administering potassium chloride 2 to 4 grams daily

(6) *Mental Changes* Real psychotic changes are rare but euphoria depression insomnia nervousness and mania may occur

(7) *Alkalosis* (metabolic) from sodium retention

(8) *Adrenal Cortical Overstimulation* Moon face hirsutism red striæ osteoporosis ecchymoses may occur The dose should be reduced if possible

(9) *Delayed or inhibited wound healing*

(10) *Reactivation* of a tuberculous focus

(11) *Acne*

Contra indications to Therapy with A C T H and Cortisone

(1) Hypertension

(2) Diabetes Cortisone and A C T H however can be given if the insulin dose is increased

(3) Chronic nephritis

(4) Known psychotics and psychopathic personalities

(5) Cushing s syndrome

(6) Congestive heart failure

(7) Hirsutism

(8) Tuberculosis

Dosage Recent reports indicate the minimum satisfactory dosage of Cortisone is 100 mgms daily for six days a week There appears to be little need for the original booster doses of 300 mgms and then 200 mgms on the first and second days respectively The dose is given once daily In those who do not respond it appears that larger doses will be necessary and these larger doses carried on over relatively long periods appear to cause few ill effects apart from water retention and mild Cushing s syndrome The best results seem to be obtained in early and moderate cases who require smaller doses of the hormone and for whom the protracted maintenance dose can be reduced to a minimum

With A C T H the minimum satisfactory dose appears to be 10 mgms four times daily—but the dose may be increased to 25 mgms five times daily when metabolic alterations are more common

(4) Changes in electrolyte balance—namely retention of sodium and chloride with increased excretion of potassium calcium and phosphates The latter changes may be associated with decreased chondrogenesis and osteogenesis with a reduction in plasma alkaline phosphatase

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	Lœffler's syndrome
	Acquired hæmolytic jaundice
Some effect is also reported in —	
(5) Diseases of the Eye	Acute iritis
	Acute keratitis
	Acute uveitis
	Acute choroiditis
	Acute conjunctivitis
(6) Skin Diseases	Contact dermatitis
	Exfoliative dermatitis
	Pemphigus
	Psoriasis
(7) Renal Diseases	Acute glomerulo nephritis
	Nephrosis and Nephrotic syndromes
(8) Alimentary Diseases	Chronic ulcerative colitis
(9) Blood Diseases	Acute leukæmia
	Chronic lymphomas
	Multiple myeloma
	Early aplastic anæmia
	Agranulocytosis
(10) Miscellaneous	Beryllium granulomata
	Delirium tremens

The Use of A C T H as a Test of Adrenal Functions

First reported by Thorn and now known as the Thorn Test

Basis —An injection of 25 mgms of A C T H produces a reduction in circulating eosinophils and an increase in the uric acid/creatinine ratio

The normal circulating eosinophils are ±200/cmm—results are expressed as a per cent of the initial count or level

A per cent fall of 50 per cent or more of eosinophils below injection level and an increase of 50 per cent or more in the uric acid/creatinine ratio indicate a satisfactory adrenal cortical response

Applications of Thorn Test 1 In suspected adreno cortical insufficiency

2 Test of adrenal reserve pre or post operatively based on the following —

(1) Normally there is an almost complete disappearance of circulating eosinophils 24–48 hours after a major operation

(2) Usually there is a sharp rise in eosinophils on the second and third post operative day

Thus the finding of a high eosinophil (or normal) level 24–48 hours post operatively suggests adreno cortical insufficiency A negative

Six hourly dosage is preferable to eight hourly Once satisfactory results are obtained, gradual reduction can be made until the patient is on the minimum dose at the longest interval—this averages 15–20 mgms twice daily

The Control of Therapy From observations in large series and from our own small experience, it seems unnecessary to control the dosage scheme with such extensive biochemical procedures as previously but the E S R and the hæmoglobin are good laboratory indications of the patient s progress

Assessment of clinical improvement is most important, and this may be done subjectively and objectively by measuring joint movement, tenderness of joints by direct pressure and by the blood pressure cuff method

The Anti rheumatic effects of Cortisone and A C T H The first symptoms to subside are muscular and articular stiffness and rest pain Next there is a loss of demand for analgesics Subsequently joint pain on motion lessens, joint movement improves, and tenderness decreases Later still comes reduction in joint swelling, effusions and mild flexion deformities with improvement in muscle strength Improvement appears to occur earlier with A C T H therapy than with Cortisone

General constitutional changes occur early and include euphoria reduction in fever loss of toxic feeling increased appetite with corresponding increase in weight

The Diseases in which Cortisone and A C T H have been shown to have a beneficial effect

(1) Rheumatoid Group	Rheumatoid arthritis
	Juvenile rheumatoid arthritis
	Ankylosing spondylitis
	Psoriatic arthritis
(2) Systemic Collagenoses	Rheumatic fever
	Polyarteritis nodosa
	Disseminated lupus erythematosus
	Dermatomyositis
	Scleroderma
(3) Metabolic Disorders	Gout (Given with Colchicine)
	Idiopathic hypoglycæmia
	Adrenal insufficiency (acute chronic)
(4) Hypersensitivity Diseases	Bronchial asthma
	Hay fever
	Contact dermatitis
	Drug sensitivity
	Giant urticaria

Since rheumatoid arthritis does not terminate fatally the small number of autopsy studies available is in part responsible for continued lack of progress in this direction

In 100 consecutive cases of pure rheumatoid arthritis the writer has found clinically eight with co existent rheumatic carditis and has further notes of 30 cases where rheumatic carditis (mainly mitral stenotic valvular lesions) has co existed This is in sharp contrast to the extremely high incidence of rheumatic carditis complicating rheumatoid arthritis found by others at autopsy Baggenstoss and Rosenberg (1941) found 53 per cent Bayles (1943) 26 per cent Fingerman and Andrus (1943) 31 per cent and, highest of all 65 per cent in Young and Schwedel s series (1944) The most recent study is by Bradfield and Hejtmancik (1950) who analysed the cardiac condition of 45 patients under 50 who were suffering from rheumatoid arthritis in which seven (15 5 per cent) had definite clinical X ray and electro cardiographic evidence of cardiac damage in spite of few of them having symptoms referable to the heart

Bywaters (1950) on the other hand set out to examine the relationship between rheumatic fever and rheumatoid arthritis on the basis of a series of cases at the British Postgraduate Medical School with biopsy or autopsy methods available and his conclusions definitely favour the existence of two separate diseases In a series of 27 autopsies of rheumatoid like arthritis including Still s disease but excluding spondylitis ankylopoietica 19 had no relevant cardiac lesions and of the remaining eight three had evidence of rheumatoid cardiac lesions and five (18 per cent) manifested rheumatic heart disease According to his criteria in this small series the incidence of rheumatic heart disease complicating rheumatoid arthritis proper is seven per cent Bywaters states that following rheumatic fever there is a type of chronic secondary polyarthritis first described by Jaccoud which can be distinguished from rheumatoid arthritis by among other features —

(a) The history of true rheumatic fever and its migratory nature the initial polyarthritis the presence of chorea the development of heart lesions or the response to the salicylates

(b) There is a flexion deformity of the metacarpophalangeal joints with some periarticular soft tissue swelling over them and the wrist with ulnar deviation and/or subluxation affecting the fourth or fifth fingers sometimes with radiological evidence of erosion of the metacarpal heads

(c) The disease is relatively inactive with a normal sedimentation rate

(d) Unlike true rheumatoid arthritis the synovial membrane is normal and there is evidence of fibrosis of the capsule The

response to the Thorn Test pre operatively suggests reduced adrenocortical function

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RHEUMATOID HEART DISEASE

Clinicians such as Hutchinson and Poynton upheld the unitary theory of the rheumatic diseases basing their opinions on analagous clinical bacteriological histological and biochemical findings in rheumatic fever and the rheumatoid type of arthritis Three debatable questions recur —

(*a*) Is the co existence of rheumatoid disease and rheumatic carditis a coincidence or a somewhat rare combination of two distinct clinical entities ?

(*b*) Are they present concurrently or was the rheumatoid disease preceded by acute or subacute rheumatism ?

(*c*) Can certain types of rheumatic fever produce as Bywaters (1950) has recently suggested a chronic rheumatic joint disease distinct from rheumatoid arthritis ?

In our view the number of borderline cases lying between acute rheumatism and rheumatoid disease including its arthritic manifestations, lends further weight to the unitary theory

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RHEUMATOID LUNG DISEASE

Ellman and Ball (1948) described three cases of rheumatoid lung disease in support of the many pathological other than joint changes which may occur in various tissues and organs in these rheumatoid granulomatous diseases of the collagen matrix The experimental production in rheumatic fever of anaphylactic pulmonary lesions with a peculiar type of pneumonitis has received attention (Rich and Gregory 1943) and pulmonary lesions are known to occur among allied systemic collagenoses like polyarteritis nodosa (Miller and Daley 1946) and disseminated lupus (Rakov and Taylor 1942 Klemperer 1948) The three cases we have described exhibited common features in what appears to have been the development of lung lesions during the early active phase of the rheumatoid joint lesion We have considered it reasonable to postulate a hypersensitivity phenomenon involving equally the joint and lung tissues The clinical course was uniform the joint lesions preceding the pulmonary involvement both being no doubt manifestations of the same pathological process *Histological study of the lungs in two cases that came to necropsy* presented certain common features fibroblastic thickening of the alveolar walls (chronic fibrosing pneumonitis) together with infiltration by mononuclear plasma and occasional polymorphonuclear cells (Fig 40) In association with necrosis found in the muscular wall of the artery in other parts of the body this suggested a previous acute arteritis as part of a fibrinoid necrosis

Since reporting these cases others of an analogous nature have come under our care and further cases have been reported by Hart (1948) Leys and Swift (1949) and Schlesinger (1949) Baggenstoss and Rosenberg (1943) report pleural involvement in 73 per cent of a series and it is possible that serous as well as synovial membranes may be attacked by the same ætiological agent

Jaccoud type of polyarthritis, as Bywaters admits is relatively rare but he believes that in three of these five cases the joint lesions were probably of the Jaccoud type



FIG 39 Hands from a case of probable chronic secondary polyarthritis (Type Jaccoud) which has persisted for 2 years after the attack of acute rheumatic fever There are (1) swellings of proximal interphalangeal joints and ulnar deviation and ( ) relatively inactive disease with a normal sedimentation rate

Two such cases have been seen by the author during the past few years (Fig 39) In our series joint lesions of arthritis which have occurred in association with the heart lesion have been mainly of the rheumatoid arthritis type

In a few cases that exhibit gross subcutaneous necrobiotic nodules these may also be found in the pericardium and heart muscle Pericarditis with or without effusion is known to occur sometimes as the only form of "rheumatoid heart disease" In Still's disease pericarditis has been described by *Still Schlesinger Bywaters* and others

It is our opinion therefore that while a chronic secondary polyarthritis (type Jaccoud) closely simulating rheumatoid arthritis can occur following and be related to rheumatic fever the majority of cases of rheumatoid arthritis exhibit a benign rheumatoid heart disease often structurally indistinguishable from the carditis of rheumatic fever (apart from the rarer nodular granulomatous lesions and pericarditis) and this suggests that rheumatoid disease and rheumatic fever may prove to be different manifestations of a common fundamental morbid process possibly of allergic origin

Committee of the Empire Rheumatism Council the mean was 42 years for males and 41 for females but cases are sometimes seen in childhood and in old age The view commonly stated in the literature that rheumatoid arthritis has a predilection for young women was not *supported by the investigation to which we have already referred* The disease may be insidious or sudden in onset but unfortunately more frequently the former Unfortunately because early attention is seldom sought and early diagnosis and treatment are the exception rather than the rule For example of 100 consecutive cases of rheumatoid arthritis the average duration of the disease before advice was sought was 6 1 years the longest period being as much as 25 years and the shortest six months On the other hand when the onset is acute there may be gross loss of weight general malaise anorexia profuse sweating palpitation etc and the general constitutional aspect may so overwhelm the local manifestation as to constitute a real problem in diagnosis During the war more particularly acute fulminating cases in both sexes were seen where it was extremely difficult to differentiate the condition from rheumatic fever In a few cases there has undoubtedly been a condition of rheumatic fever *flowing over as it were into acute rheumatoid disease with established* joint manifestations Such an acute onset occurring in some five to ten per cent of cases accompanied by a temperature ranging from 100 to 103° F is found principally in younger subjects and may last from one to six months In the Empire Rheumatism Council s investigation the onset was acute in 44 per cent of cases and 17 per cent of patients were febrile

In the insidious type of case the prodromal symptoms include progressive loss of weight general malaise tachycardia anorexia fleeting joint pains and swellings paræsthesiæ of hands and feet and febrile attacks for as long as a year or even more before established joint damage has occurred This long incubation period must be recognised as a pre arthritic syndrome if early diagnosis is to be made and treatment instituted Patients look ill toxic and wasted They are usually asthenic and many exhibit vaso motor phenomena such as cold extremities and Raynaud s phenomenon We have (Ellman and Weber 1948) described a case of juvenile rheumatoid arthritis with a mild sclerodactylia a Raynaud phenomenon and typical calcinosis circumscripta The association of a rheumatoid type of arthritis with Raynaud s phenomenon and occasionally with conditions such as rheumatic fever scleroderma intermittent hydroarthrosis palindromic rheumatism disseminated lupus and even Sjogren s disease (kerato conjunctivitis) (Ellman and Weber 1949) is noteworthy It is possible as Bywaters (1949) has stated that their resemblances are more important than their differences There may be anæmia of the

Our clinical impression, not yet verified statistically, is that the incidence of pulmonary tuberculosis is higher in the rheumatoid subject than in the general population

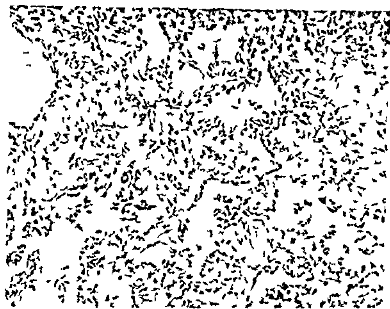


FIG 40 Microphotograph of interstitial pneumonitis with well marked fibrosis between the lung alveoli [×100]

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CLINICAL MANIFESTATIONS OF THE RHEUMATOID TYPE OF ARTHRITIS

Systemic Manifestations The disease with the exception of ankylosing spondylitis occurs preponderantly in women between 20 and 45 In the controlled investigation of the Scientific Advisory

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ELLMAN, P., WEBER, F. P., and GOODIER, T. E. W. (1951). Contribution to the pathology of Sjogren's disease. *Quart. J. Med.*, 20, 33.
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ATYPICAL FORMS (VARIANTS) OF RHEUMATOID DISEASE

There are certain atypical forms of rheumatoid disease worthy of particular note whose similarities rather than their differences hitherto unduly accentuated which merit of more extensive clinical research from an ætiological standpoint.

Still's Disease. Described by Still in 1897, this manifestation of rheumatoid arthritis in childhood (which has been seen in a child of only three years) is characterised by fever, polyarthritis, lymphadenopathy, splenomegaly and sometimes hepatomegaly. Cardiac complications are relatively common and several of Still's original cases exhibited pericardial involvement. The disease is often acute and the rapid onset of joint deformity may require immediate attention, but the general lines of treatment are similar to those described in respect of rheumatoid disease generally. Schlesinger (1949) has recently recorded 20 such cases, drawing attention to the widespread nature of the disease. In some there was high fever and severe leucocytosis, in others a leucopenia, and in others still migratory urticarial or maculo-papular rashes, lymphadenopathy, pleurisy and pneumonia with or without pericarditis. Nine cases had enlarged liver and spleen and four cases had jaundice. Finally, Still's disease may on rare occasions terminate in lymphatic leukæmia.

Felty's Syndrome. This adult syndrome corresponds closely to the Still syndrome of childhood. Emaciation, intermittent fever, splenomegaly, occasionally hepatomegaly, lymphadenopathy, hypochromic anæmia, leucopenia (varying from 800 to 3 000 white cells per cubic millimetre) and pigmentation of the skin may all occur. One case under our care had a pulmonary complication akin to a miliary lung lesion. Splenectomy has been reported as reacting favourably on the arthritis (Hutt, Richardson and Staffurth, 1951) and has also been tried in rheumatoid and Still's disease (Zimmer, 1945). We are doubtful if it is really justified.

Psoriasis Arthropathica. Experience of cases of rheumatoid arthritis combined with psoriasis and sharing a common mode of onset, exacerbations and remission has led to the conviction that this

hypochromic type with leucocytosis or leucopenia. The family incidence is sometimes striking as in the example of two sisters aged 40 and 44 years, both of whom suffered from rheumatoid disease confined to the knee joints while a third sister suffered from rheumatic carditis.

Other constitutional disturbances which may occur are muscular weakness and atrophy, cutaneous changes, cutaneous and subcutaneous nodules varying in size from that of a pea to that of a walnut, visceral changes such as lymphadenopathy, splenomegaly and occasionally hepatomegaly as seen in the so called Still and Felty syndromes. Nodules appear principally on extensor surfaces of the forearm and the incidence would appear to be between 10 and 20 per cent. The histological similarity of the nodules of rheumatic fever and the acute transient nodules of rheumatoid arthritis is particularly noteworthy. There may also be cardiac and eye lesions. In connection with the latter Sorsby's (1946) eye investigations demonstrated an incidence of iritis in rheumatoid arthritis higher than hitherto recognised. The condition was mild and mainly unilateral but assessed against a control series, three cases were found among patients suffering *from* ankylosing spondylitis and 15 out of 332 cases of rheumatoid arthritis. He concluded that there was some parallel in the reaction of the eye and the joint to a noxious agent. In the osteo arthritic type the incidence of iritis was not significant. Finally, achlorhydria, raised sedimentation rate and diminished Vitamin C excretion in the urine may all occur while on the other hand there are a limited number of cases with scarcely any systemic manifestations.

Local Manifestations. The majority of sufferers complain chiefly of the local manifestations of the disease, swelling and limitation of movements of the joints. In order of frequency the joints involved are proximal interphalangeal, wrists, metacarpophalangeal, toes, knees, elbows, shoulders (mainly periarticular), ankles, hips, sterno clavicular and temporo mandibular joints. The pain, swelling and stiffness are often migratory or intermittent and variable in duration and degree. All too frequently the patient, becoming acclimatised to the discomfort comes to ignore it until migratory signs are replaced by permanent pain, swelling and stiffness, by which time atrophy, ankylosis or deformity may be present.

Where the process is of an acute nature muscle, nerve tissue, cutaneous, subcutaneous and fibrous tissue including tendons may also be involved, while visceral manifestations are well recognised.

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In the established case osteoporotic changes occur in the bodies of the vertebræ and around the bone in the neighbourhood of the sacro iliac joints, while calcification of the intervertebral joint capsules anterior and lateral spinal ligaments and costo vertebral joints takes place. The radiological appearances in this late stage are those of the characteristic 'bamboo spine'. In these advanced cases the disease is probably inactive and the prognosis bad but in active cases early diagnosis and treatment on lines analogous to those prescribed for the rheumatoid type of arthritis have revolutionised the outlook. Nevertheless the long term nature of the treatment must be recognised from the outset, and a sanatorium regime advised with the patient in bed during the active stage. In bed one head pillow should be allowed while a firm non sagging mattress should be reinforced by fracture boards beneath. If ankylosis is inevitable, the ideal position is that in which the patient when upright can look straight ahead (cf Fig 42). Hitherto patients have been placed in serial plaster shells with the object of (*a*) correcting abnormal posture and (*b*) maintaining a normal one but recently local X ray therapy has proved so effective in reducing spasm relieving pain improving the range of movements and controlling activity that plaster shells are tending to be discarded. This new application of X ray therapy is now under review and while the questions of dosage control and prevention of ill effects are the concern of the expert it would seem that in this direction there lies a definite promise of avoiding the gross disablement ordinarily associated with the disease. It should be noted that ankylosing spondylitis in contradistinction to the rheumatoid form of arthritis does not respond to gold therapy while X ray therapy has



Fig. 43. Photograph of a young male adolescent with severe ankylosing spondylitis. He also had an acute iritis and soft tissue swelling of the left ear. His cervical, dorsal and lumbar spines as well as his sacro-iliac, costo-vertebral and costo-transverse joints were completely ankylosed and his only field of vision was the floor due to his flexion deformity of the neck.

association should be regarded as a clinical entity The effect of gold therapy and more recently Cortisone and A C T H in this connection has been particularly interesting and where the joint response has been good there has been corresponding improvement in the psoriatic lesion (Fig 41)



Fig 41 Case of psoriasis arthropathica Note rheumatoid joint *changes in hands knees and feet*

Ankylosing Spondylitis (Spondylitis ankylopoietica spondylitis *rhizomelique* spondylitis of Marie Strumpell and von Bechterew) Unlike the rheumatoid type of arthritis this occurs predominantly in male adolescents (of 50 consecutive cases only three were females) It is however regarded by many as a spinal manifestation of rheumatoid disease with which it has much in common although it is *often* regarded as a separate entity

The Thorax in Ankylosing Spondylitis The importance of the reduction of thoracic expansion due to involvement of the costo transverse and costo vertebral joints in ankylosing spondylitis is well recognised but it is perhaps not equally appreciated that all the components of thoracic expansion with the exception of the diaphragm may sooner or later become involved by this disease In advanced cases thoracic movement is usually grossly restricted *although* long standing cases with involvement of sacro iliac joints and hip joints and a bamboo spine yet with a moderately good thorax do occur This thoracic involvement with a diminished vital capacity and chest expansion is *often* of considerable diagnostic importance (Hart *et al* 1950) Exertional dyspnoea may be a major symptom and the case may be referred to a chest hospital

The familial incidence of the disease is noteworthy for we have had under our care two brothers and two sisters with the disease Hence when one case is discovered it is a *wise procedure to investigate other* members of the family

during the last decade While the classical triad is regarded as diagnostic on occasions the clinical pattern may vary and may be accompanied by ulcerative colitis with severe bloody diarrhœa and a crusted psoriasiform skin lesion known as keratodermia blenorrhagica (Fig 43) The bilateral conjunctivitis which becomes purulent usually subsides within seven to ten days and is rarely complicated by scleritis iritis or keratitis and even these usually clear up without leaving sequelæ The urethritis associated with abacterial pyuria usually clears within a month although the picture may sometimes be complicated by lesions on the glans penis (balanitis circinata) The ætiology of the condition remains obscure dysentery a virus and a pleuro pneumonia bacillus having been variously incriminated Laboratory investigations usually confirm a hypochromic anæmia with a mild leucocytosis of about 12 000 and a raised sedimentation rate Culture and serological tests reveal no significant findings The prognosis is usually good the illness lasting from a few weeks to several months and then clearing completely Chemotherapy with penicillin and sulphonamides may be tried but are not usually effective Hormone therapy promises to produce rapid reversibility

Palindromic Rheumatism Hench and Rosenberg (1944) describe a syndrome of multiple recurrent attacks of painful inflammation affecting joints and neighbouring tissues One or more joints may be involved in these episodes which appear suddenly, last a few hours or days and then subside completely without residual damage The ætiology is unknown and the condition is not common Almost all joints are liable to attack although there is a distinct predilection for the finger joints Periarticular and para articular attacks occur in soft tissues in some cases and the heels finger pads distal phalanges thumb pad dorsal surfaces of forearms and region of the Achilles tendon were observed to be favourable sites in the cases described by Hench and Rosenberg In severe instances intracutaneous and subcutaneous nodules have been observed in the thumb pads on the fingers palmar fascia and over the wrist There are few constitutional reactions either during or between attacks which recur either daily or several times a year leaving no clinical radiological or pathological changes in their train The blood count blood chemistry and X ray findings remain normal throughout except for a relative lymphocytosis and raised sedimentation rate during an attack During these phases the synovial membrane shows an inflammatory reaction with acute cellular exudates in the synovial cavities comprising mainly polymorphs and fibrin In only three of Hench s 34 cases was there an eosinophilia As noted elsewhere (Ellman and Ball 1948) it is possible that the syndromes of a recurrent and transitory nature included under the term palindromic rheumatism can be extended to include as Parkes

not as yet produced any appreciable effect on the latter Cortisone and ACTH promise to be successful in the treatment of selected cases of this condition

Chronic Absorptive Arthritis This is variously described as "opera glass hand" "main en lorgnette" or "arthritis mutilans" Solomon and Stecker (1950) maintain that it is less rare than is generally assumed The onset is similar to that of a pure rheumatoid developing so rapidly that the patient is helpless and bed ridden in a relatively short time In contra distinction to the pure rheumatoid condition the fingers or wrists are shortened and have an abnormal range of movement in all directions The capacity of the fingers to elongate like a telescope when pulled out is a striking feature and the skin instead of being contracted thin atrophic shiny and pale is loose wrinkled and thickened



Fig 43 The ankles and feet from a case of Reiter's syndrome in a young male who also had a crusted skin lesion on the feet and nails due to keratodermia blenorrhagica

Reiter's Syndrome The syndrome of acute polyarthritis of young males associated with non gonococcal non specific urethritis and conjunctivitis has received considerable attention in the literature

during the last decade While the classical triad is regarded as diagnostic on occasions the clinical pattern may vary and may be accompanied by ulcerative colitis with severe bloody diarrhœa and a crusted psoriasiform skin lesion known as keratodermia blenorrhagica (Fig 43) The bilateral conjunctivitis which becomes purulent usually subsides within seven to ten days and is rarely complicated by scleritis iritis or keratitis and even these usually clear up without leaving sequelæ The urethritis associated with abacterial pyuria usually clears within a month although the picture may sometimes be complicated by lesions on the glans penis (balanitis circinata) The ætiology of the condition remains obscure dysentery a virus and a pleuro pneumonia bacillus having been variously incriminated Laboratory investigations usually confirm a hypochromic anæmia with a mild leucocytosis of about 12 000 and a raised sedimentation rate Culture and serological tests reveal no significant findings The prognosis is usually good the illness lasting from a few weeks to several months and then clearing completely Chemotherapy with penicillin and sulphonamides may be tried but are not usually effective Hormone therapy promises to produce rapid reversibility

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Weber (1946) has suggested the so called intermittent hydro arthrosis serum joint disease allergic arthritis and allied syndromes We have observed two cases of ' palindromic rheumatism which have actually developed established rheumatoid disease and this is in keeping with the experience of Ropes (1944) Kuhns (1945) and, to some extent Bywaters (1949)

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PSYCHOSOMATIC ASPECTS OF CHRONIC NON ARTICULAR RHEUMATISM

Non articular rheumatism embraces some 75 per cent of cases of chronic rheumatic disorders including fibrositis muscular rheumatism neuritis panniculitis capsulitis pleurodynia and lumbago The term ' fibrositis is applied to many maladies sharing a common symptomatology of pain stiffness and limitation of movement and the status of fibrositis and backache with particular reference to the problem of differential diagnosis has been reviewed by Ellman (1947) Valentine (1947) and Cohen (1948)

It has long been recognised that emotional factors play an important role Halliday (1944) found that 30 per cent of 145 consecutive patients labelled as having rheumatism were incapacitated because of psychoneurosis and that psycho neurotic rheumatism accounted for 40 to 60 per cent of those who remained on the sick list for two months or more Ellman and others (1942) in a study of fifty ' fibrositis patients with a history of three months or more made psychiatric diagnoses in 38 (76 per cent) Flind and Barber (1945) found that in about 42 per cent of patients admitted to R A F special rheumatic centres the disability was essentially psychogenic Such ' psychogenic rheumatism was the most frequent cause of disability

(34 per cent) in 450 soldiers with rheumatic complaints admitted to U S military hospitals (Boland and Corr 1943) Hench and Boland (1946) in a review of rheumatic disorders affecting American soldiers in the second world war claimed that 15 to 20 per cent of men admitted to special rheumatism centres were in fact suffering from psychogenic rheumatism They stress the importance of recognising this psycho neurosis affecting the locomotor system— a musculo skeletal expression of functional disorders They assert that this is one of the commonest causes of localised aches and pains in muscles and joints in both civilian and military life and attempt a differentiation on clinical grounds between what they term primary fibrositis and psychogenic rheumatism

Boland (1947) elaborating this conception refers to Weiss who remarked on the significance of smouldering discontent in such cases Hench (1946) Tegner and others (1949) draw attention to the same problem Investigating the subject from a different angle Edmonds (1947) reported that muscular pains were prominent in 47 per cent of a series of 183 psychoneurotics

Ellman and Shaw (1950) have studied 109 cases (78 women and 31 men) of chronic non articular rheumatism over a period of four years 1943 to 1947 Their ages ranged from 19 to 68 years 44 being the average They were mainly drawn from the artisan class All had a history of attendance at a Rheumatism Unit for six months or more and all were given a full clinical radiological and pathological examination The diagnosis of non articular rheumatism was made largely *by exclusion investigation having failed to reveal abnormal physical* signs of rheumatic disease In the few cases where some abnormality was found—e g mild or very early evidence of degenerative joint disease on X ray examination—it was considered insufficient to account for the symptomatology Every case was also examined psychiatrically

A series of 58 controls (34 women and 24 men) of comparable age and social class was subjected to similar physical and psychiatric examinations The patients had been variously diagnosed initially as suffering from chronic fibrositis lumbo sacral strain postural deformity low backache functional backache capsulitis or bursitis peri arthritis sciatic pain and degenerative arthritis In a few the diagnosis of rheumatoid arthritis had been made and four female patients none of whom now had signs of active rheumatic disease had been given courses of gold treatment

The following conclusions were reached —

(1) In 109 cases of chronic non articular rheumatism no evidence *of active rheumatic disease* was found in spite of the very long duration of symptoms

(2) There was a family history of neuropathy and psychopathy in 49 per cent of cases as compared with 14 per cent of controls and an incidence of early neurotic traits and previous nervous breakdown in 48 per cent of cases as compared with 21 per cent of controls

(3) Evidence of significant emotional stress just prior to the onset of symptoms was found in 27 per cent of cases as compared with 11 per cent of controls

(4) The predominant type of personality among the patients was the over anxious inhibited obsessional

(5) In 79 per cent of cases there was evidence of a significant personality disturbance or of a frank neurosis

(6) Half the cases showed anxiety states usually linked with considerable tension Frustration and resentment in a disturbing environmental situation were common

(7) Evidence has been adduced to show the importance of neurosis or predisposition and of the "focussing" effect of previous injury or disease of the muscles and joints in the patient and his family

It seems clear that the nature of this often very prolonged incapacity is psychiatric in the majority of cases The "rheumatism" with its chronic aches and pains is merely part of the neurotic disorder

If therefore "chronic non articular rheumatism" frequently arises from a psychosomatic disorder adequate facilities for the investigation of the psychiatric factors involved must be included in the national schemes devised for the prevention and treatment of rheumatism and the necessity for looking beyond the muscles and ligaments to the home family and place of work should be recognised by practitioners In general there should be no difficulty in persuading patients to accept the role played by emotion in the causation and development of their illness Many are quite suitable for out patient psychiatric treatment by psychotherapy supported where necessary by sedation others will require in patient treatment in the psychiatric ward of a general hospital or in neurosis centres

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GOUT

We propose to confine our attention to some recent studies on this long established disease which was first separated in the seventeenth century from the acute and chronic rheumatic diseases by Sydenham whose personal experience of the condition has become a classic of clinical definition In 1859 A B Garrod added much to existing knowledge while comparatively recently American workers have investigated the clinical and metabolic as well as the genetic and endocrine aspects In this country Henry Cohen (1948) has made a major clinical contribution to the subject The essential problem of ætiology remains however unsolved

Modern work confirms the significance of the hereditary factor for gout is a familial malady in which the family tree must be perused as skilfully by the physician as by the genealogist (Talbott 1943) Juvenile gout is invariably due to an hereditary predisposition based on hyperuricæmia For example a patient aged 56 had recurrent attacks of acute gout his father suffered from advanced chronic deforming gouty arthritis and his son aged 16 in the course of a routine health examination was found to have an asymptomatic hyperuricæmia with a serum acid of 9 5 mgm per cent

Recent genetic studies by Smyth Cotterman and Freyberg (1948) and Stecker Hersh and Solomon (1949) have been reviewed by Smyth (1951) who has summarised as follows the present status of the genetic factor in gout and hyperuricæmia

(a) Asymptomatic hyperuricæmia is frequently found among relatives of patients with gout

(b) Gouty arthritis may develop in an individual of either sex with serum urate level sufficiently elevated for a sufficient time this occurring less frequently in women owing to their lower normal level and to the lesser effect (i e lower penetrance) of the pathological gene in this sex

The prevailing idea that gout is on the decline is probably unsound although fewer advanced cases are encountered today Sedentary workers are more commonly affected than labourers while women of

all social groups are rarely affected With regard to the precipitating aetiology of gout its apparent decline in incidence and severity cannot be dissociated from growing moderation of habits In other words the diathesis is probably transmitted as before but port drinking and high living and heavy consumption of beer by brewers' draymen are to day rare Even without statistical evidence this in itself indicates a definite social change Since the condition may simulate either the rheumatoid or the osteo arthritic type of arthritis more accurate diagnosis may be partially responsible for the lower figures of the present time Moreover there are some who hold the view that not only is gout a metabolic disease but that rheumatoid disease may be of similar origin and that its pathogenesis may in the future yield more positive results on a biochemical and allergic basis The favourable response to hormone therapy in these two diseases is not without significance in this connection

Hench has claimed that patients with gouty arthritis constitute no less than five per cent of all arthritides seen at the Mayo Clinic In his chart of the natural history and course of the disease he has enumerated 21 points to aid in diagnosis which should be considered in relation to —

(a) The difficult asymptomatic phase before the manifestation of joint involvement

(b) The articular phase whether acute or chronic when two or more of the following features are almost certainly diagnostic

(1) A family history

(2) A history of recurrent attacks of acute joint pain with wholly asymptomatic intervals (especially in a male over 40)

(3) Acute joint symptoms associated with renal colic or nephritis

(4) A serum uric acid above 6 mgms per cent (Normal whole blood 2–4 mgm per cent serum 3–5 mgm per cent)

(5) A good response to colchicine (with or without cortisone or A C T H)

(6) The presence of tophi or olecranon bursitis

(7) Characteristic X ray changes notably in the great toe although absence of X ray change does not exclude gout

Cortisone and A C T H in Gout Recent studies have implicated the pituitary adrenocortical mechanism in gout and gouty arthritis and American workers (Hellman 1949 Boland 1950) have shown that attacks of acute gouty arthritis can be either precipitated or aborted by these two chemotherapeutic agents As Smyth (1951) has already noted these hereditary studies have also established that —

(1) The average normal plasma urate concentration in males is higher by approximately 1 mgm per cent than in females

(2) This difference in plasma urate concentration is also present in gouty patients and their relatives Thus in males who inherit asymptomatic hyperuricæmia the average plasma urate level is higher than in females who inherit this gene

(3) *Males who inherit asymptomatic hyperuricæmia do not gener*ally develop abnormally elevated plasma urate levels until after puberty Female carriers of genetic hyperuricæmia do not ordinarily develop such levels until just before or after the menopause

In America Thorn *et al* (1950) Hellman (1949), Sprague *et al* (1950) have shown conclusively that when cortisone and A C T H are administered to gouty subjects they induce a transitory increase in the excretion of uric acid (although the mechanism that produces this effect is not yet known) and a drop in the serum uric acid Simultaneously the urinary output of 17-ketosteroid is greatly diminished giving further evidence of the endocrine aspect of gout an aspect of particular significance in relation to treatment

Treatment If gout is recognised as an hereditary disease its prevention is in the first instance a eugenic problem It is as Sydenham has stated incurable yet it responds remarkably well to a properly disciplined regime particularly if this can be instituted at an early stage For acute attacks bed rest should be prescribed with immobilisation and protection of the involved joint by light splinting and a bed cradle Applications of heat or cold are known to be helpful in varying degrees *Colchicine* 1/120 gr by mouth every hour until pain is relieved has hitherto been the sheet anchor of treatment Toxicity is indicated by diarrhœa nausea and vomiting but as a rule *eight to ten tablets can be given in 24 hours before diarrhœa occurs* and this dosage is usually adequate to control the most persistent pain

However since Hellman (1949) reported dramatic control of symptoms of acute gout with A C T H within periods varying from 6–48 hours and Boland (1950) recorded a similar control with cortisone a new field of therapy has been discovered * To date however experience shows exacerbation of symptoms when these preparations are discontinued To counteract such exacerbations Wolfson and Cohn (1950) have recommended a combination of colchicine with the hormone therapy and have advised an appropriate schedule which appears to be very effective in the treatment of acute attacks

* It should be noted that when these hormones are given during the intercurrent quiescent phase an acute attack of gouty arthritis may be precipitated

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